EPA-SAB-EC-99-0XX

Honorable Carol M. Browner
Administrator
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, DC 20460

Subject: Review of Revised Sections of the Proposed Guidelines for Carcinogen
Risk Assessment

Dear Ms. Browner:

1   At the request of the Office of Research and Development (ORD), a Subcommittee of the

2   Science Advisory Board's (SAB) Executive Committee (augmented with representation from the

3   Scientific Advisory Panel), reviewed selected sections of the Proposed Guidelines for

4   Carcinogen Risk Assessment (GLs). The Committee subsequently met in Washington, DC, on

5   January 20-21, 1999 and generated the report discussed below.

6

7   The SAB's 1997 review (EPA-SAB-EHC-97-010) of the 1996 Proposed Guidelines for

8   Carcinogen Risk Assessment generally commended the efforts of the Agency to update its GLs in

9   keeping with new scientific information and commentaries by authoritative groups (e.g., the

10   Presidential/Congressional Commission Report on Risk Assessment and Risk Management in

11   Regulatory Decision Making(GPO #055-000-00568-1, 1997). However, the review also

12   identified a number of areas where further improvements/clarifications could be made - hazard

13   descriptors, the use of mode of action information, and dose response (DR) analysis. These

14   particular sections contained the Agency's response to recommendations contained in the SAB's

15   1997 review of the GLS as proposed in 1996. EPA consequently revised selected sections of the

16   GLs to respond to these comments and discussions within the Agency. These revisions to the

17   GLs were reviewed by the Subcommittee at a meeting held in Washington, DC, on January 20-21,

18   1999 and addressed in this report.

19

20   The Charge for this review (see section 2.2 of the enclosed report for the complete

21   Charge) addressed the adequacy of the proposed narrative summaries and hazard descriptors as a

22   basis for characterizing the evaluation of carcinogenic potential; the use of Mode of Action

23   (MOA) information; the use of DR analysis as a basis for calculating the point of departure; and

24   the use of margin of exposure (MOE) analysis, including consideration of the nature of the

1 response, steepness of the DR curve, and human intraspecies variability (including susceptible
2 populations), as well as interspecies variability.
3
4   The Subcommittee's deliberations resulted in several major recommendation to the
5 Agency concerning the GLs. The first of these recommendations, although not a specific
6 technical finding, is perhaps the most important. **We believe strongly that these GLs should**
7 **become operative, as soon as judiciously possible.** The Agency has been working on the
8 revised GLs since 1990, and has sponsored several public workshops on GLs issues; the SAB has
9 held a Consultation and two reviews, with at least one more in the offing to address GLs issues
10 related to children. Clearly, there are issues noted in this report that need to be addressed and/or
11 re-visited (some continually); in addition, new ones will arise. However, it is important to
12 consolidate the progress that has been made in the current document, and have it officially issued
13 at the earliest possible date.
14
15   Other major overall findings and recommendations include:
16
17   a)   **Primacy of public health protection:** It is essential that the GLs state at the
18   outset that "..the primary goal of EPA actions is public health protection and that,
19   accordingly, as an Agency policy, the defaults used in the absence of scientific data
20   to the contrary should be health protective." These defaults should be clearly
21   explained in the revised GLs text, including the assumptions of low dose linearity
22   and the relevance of animal data to humans. The basis for the various default
23   uncertainty factors should also be clearly described.
24
25   b)   **Loss of flexibility:** The Subcommittee is concerned that EPA, in responding to the
26   SAB's 1997 request for more definition in several areas, actually reduced, rather
27   than increased, flexibility in moving from the 1996 to the 1998 version. Examples
28   included the addition of numerous new defaults, standard dose-response models,
29   restrictions on the use of the No Observed Adverse Effects Level (NOAEL)
30   approach, and fixation on the 10% excess as a point of departure.
31
32

1   c)   **Sensitive subpopulations**: EPA should include a discussion of sensitive
2   subpopulations for all agents to which the general public (as opposed to healthy
3   workers) is exposed. Although not part of this review, we wish to endorse the
4   Agency's plan to hold a meeting later this year on GLs issues related to children –
5   a most sensitive subpopulation.

7   d)   **Background and multiple exposures**: EPA should discuss the need for the risk
8   assessment to consider background exposures/processes and concurrent exposures
9   with which the chemical (mixture) of interest may display additivity or interact
10   multiplicatively.

12   Other, more specifically focused findings directly addressing the Charge include:

14   a)   The Subcommittee strongly supports the proposed "Framework" as a means for
15   providing a working model for incorporating and interpreting data in a clear and
16   transparent manner. This model was developed as part of a World Health
17   Organization working group to deal specifically with differences between the
18   approaches used by various countries to evaluate the same data with respect to the
19   risks posed by a given chemical.

21   b)   There was agreement that the narrative descriptor "known to be carcinogenic to
22   humans" or "known human carcinogen" should be retained. Although the majority
23   of the Subcommittee held that assignment to this category requires human (e.g.,
24   epidemiological) data, several Members opined that animal data demonstrating
25   strong mechanistic~~data~~ linkages between common human and animal pathways
26   could be used to support this classification.

28   c)   The use of a narrative is a key component of the hazard identification section.
29   Flexibility in how the hazard narrative is written is laudable, but a common format
30   is essential. All of the relevant data should be included.

1   d) EPA should continue efforts to achieve compatibility with international
2   organizations such as the International Agency for Research on Cancer, the World
3   Health Organization, and European regulatory bodies.

4

5   e) The Subcommittee recommended that specific criteria for judging the adequacy of
6   data on a mode of action approach are needed, and that specific examples should
7   be included to illustrate the application of these criteria.

8

9   f) The proposed GLs document remains (perhaps necessarily) vague about what
10   specific data are required to reject defaults assumptions. Some additional
11   clarification on this issue is needed. The Subcommittee does recognize that the
12   Agency does not want to be prescriptive, as the science will continue to evolve.

13

14   g) The SAB recommended in 1997 that a single risk level (e.g., 10%) be selected as
15   the point of departure for (low dose) non-linear extrapolation in order to facilitate
16   comparisons across chemicals, and provide more clarity to the risk manager. The
17   draft GLs now propose a value of 10%, while noting that, in some situations (e.g.,
18   large experiments), it may be preferable to use a non-standard value. In the
19   current Agency proposal, it is noted that a lower point for linear extrapolation can
20   be used for tumor incidence study of "greater than usual sensitivity." This is a
21   reasonable approach, and one that the Subcommittee endorses.

22

23   h) In the case of Margin of Exposure (MOE) analysis, the Subcommittee continues to
24   be concerned about the linkage between the selected risk level and the
25   incorporation of adjustment and uncertainty factors. Use of a risk level less
26   (greater) than 10% should, other things being equal, require a smaller (larger)
27   uncertainty factor. The Agency is encouraged to develop explicit guidance
28   regarding the selection of uncertainty factors for points of departure other than
29   10%. Also, because of this problem, the Agency should strive to use the standard
30   point of departure whenever possible.

31

32

1   i)   There is continuing confusion about the relationship between the LED_{10}, or ED_{10}
2   and the NOAEL. The GLs should seek to clarify, not reinforce this confusion. In
3   addition, the new GLs propose two new ten-fold adjustment factor to be used in
4   specified situations. Some Subcommittee Members questioned whether the need
5   for, or the magnitude of, these new factors is sufficiently justified in the GLs;
6   other Members supported the basic thrust of these factors, but noted that further
7   refinements were needed.

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9   We appreciate the opportunity to review these proposed revisions, and look forward to
10   receiving your response to the issues raised.

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13   Sincerely,

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18   Dr. Joan Daisey, Chair
19   Science Advisory Board

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24   Dr. Mark Utell, Chair
25   Cancer Guidelines Subcommittee

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29   ENCLOSURE

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REVIEW OF SELECTED SECTIONS OF THE CANCER RISK ASSESSMENT GUIDELINES BY THE SAB/SAP SUBCOMMITTEE ON CANCER GUIDELINES

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16 **REVISED EXEC. COMM. REVIEW DRAFT (5/20/99)**

17 **DO NOT QUOTE OR CITE**

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NOTICE

1   ABSTRACT
2
3   TO BE SUPPLIED

US EPA SCIENCE ADVISORY BOARD
CANCER GUIDELINES SUBCOMMITTEE OF THE EXECUTIVE COMMITTEE
ROSTER

January 20-21, 1999

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Dr. Mark J. Utell, Acting Chairman, Department of Medicine, Director, Pulmonary Unit, and Professor of Medicine and Environmental Medicine, University of Rochester Medical Center, Rochester, NY

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Dr. Michele Medinsky, Toxicology Consultant, Durham, NC

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Dr. Roy E. Shore, Director, Division of Epidemiology and Biostatistics, New York University School of Medicine, New York City, NY

Dr. Lauren Zeise, Chief, Reproductive and Cancer Hazard Assessment Section, Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Berkeley, CA

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Dr. Ernest McConnell, Science Advisory Panel Chair and President, ToxPath, Inc. Raleigh, NC

CONSULTANTS

Dr. Kenny S. Crump, Vice President, KS Crump Group, Inc., Ruston, LA

Dr. Lovell A. Jones, Director, Experimental Gynecology-Endocrinology, Department of Gynecologic Oncology; and Professor of Gynecologic Oncology; MD Anderson Cancer Center, Houston, TX

Dr. George Lambert, Associate Professor of Pediatrics and Director of Pediatric Pharmacology and Toxicology, University of New Jersey-Robert Wood Johnson Medical School, New Brunswick, NJ

Dr. Roger O. McClellan, President, Chemical Industry Institute of Toxicology, Research, Triangle Park, NC

Dr. James A. Swenberg, Director, Curriculum in Toxicology, Professor, Environmental Science and Engineering, Nutrition and Pathology, University of North Carolina, Chapel Hill, NC

Dr. M. Jane Teta, Director of Epidemiology, Health Information, Risk Assessment and TSCA, Union Carbide Corporation, Danbury, CT

DESIGNATED FEDERAL OFFICIALS

Ms. Roslyn A. Edson, U. S. Environmental Protection Agency, Science Advisory Board (1400), 401 M Street, SW, Room 2812M, Washington, D.C. 20460, (202) 260-8414 (202) 260-7118 (FAX) edson.roslyn@epamail.epa.gov

Mr. Samuel R. Rondberg,[1] U. S. Environmental Protection Agency, Science Advisory Board (1400), 401 M Street, SW, Washington, D.C. 20460, (301) 812-2560 (202) 260-7118 (FAX) samuelr717@aol.com (EMAIL)

EPA INTERN

Ms. Karen Martin,[2] Life Scientist, Environmental Protection Agency, Science Advisory Board (1400), Washington, DC 20460 (202) 260-6154; FAX (202) 260-7118 martin.karen@epa.gov (EMAIL)

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[1]Did not participate in the review, but served as principal editor of this report.

[2]Ms. Martin is an EPA Intern assigned to the Science Advisory Board and assisted in the conduct of this review.

1 <u>**MANAGEMENT ASSISTANT**</u>
2 **Ms. Wanda R. Fields,** Environmental Protection Agency, Science Advisory Board (1400),
3 Washington, D.C. 20460 (202) 260-5510 (202) 260-7118 (FAX) fields.wanda@epa.gov
4 (EMAIL)
5
6

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1   # 1. EXECUTIVE SUMMARY

2

3   In 1997, the Science Advisory Board's (SAB) Environmental Health Committee (EHC),

4 augmented with representation from the Scientific Advisory Panel (SAP), reviewed a draft of

5 EPA's 1996 revised Cancer Risk Assessment Guidelines (GLs) (SAB, 1997). Although generally

6 applauding the efforts of the Agency to update its GLs in keeping with new scientific information

7 and commentaries by authoritative groups, the Board identified a number of areas where further

8 improvements and clarifications could be made - hazard descriptors, the use of mode of action

9 information, and dose response (DR) analysis. EPA revised the pertinent sections of the GLs and

10 requested that the SAB review the updated materials. A Subcommittee of the SAB, including

11 representation from the SAP reviewed revised GLs at a meeting held in Washington, DC, on

12 January 20-21, 1999. The findings stemming from that meeting are addressed formally in this

13 report.

14

15   The Charge for this review (see section 2.2 for the complete Charge) addressed the

16 adequacy of the proposed narrative summaries and hazard descriptors as a basis for characterizing

17 the evaluation of carcinogenic potential; the use of Mode of Action (MOA) information; the use of

18 DR analysis as a basis for calculating the point of departure; and the use of margin of exposure

19 (MOE) analysis, including consideration of the nature of the response, steepness of the DR curve,

20 and human intraspecies variability (including susceptible populations), as well as interspecies

21 variability.

22

23   The Subcommittee developed several major recommendation to the Agency concerning the

24 GLs. The first of these recommendations, although not a specific technical finding, is perhaps the

25 most important. **We believe strongly that these GLs should become operative, as soon as**

26 **judiciously possible.** The current GLs have been around for more than a decade; the Agency has

27 been working on the revised GLs since 1990, including sponsoring several public workshops on

28 GLs issues; and the SAB has had a Consultation (SAB, 199X), the 1997 review noted above, the

29 review just completed, and one more in the offing to address issues related to children. Clearly,

30 there are GLs issues noted in this report that need to be addressed and/or re-visited, continually

31 (and new ones which will arise). However, it is important to consolidate the progress that has

32 been made in the current document, and have it officially issued at the earliest possible date.

1   Other major overall findings and recommendations are:

2

3   a)   **Primacy of public health protection:** It is essential that the GLs state at the outset

4   that "..the primary goal of EPA actions is public health protection and that,

5   accordingly, as an Agency policy, the defaults used in the absence of scientific data

6   to the contrary should be health protective." These defaults should be clearly

7   explained in the revised GLs text, including the assumptions of low dose linearity

8   and the relevance of animal data to humans. The basis for the various default

9   uncertainty factors should also be clearly described.

10

11   b)   **Loss of flexibility:** The Subcommittee is concerned that EPA, in responding to the

12   SAB's request for more definition in several areas, actually reduced, rather than

13   increased, flexibility in moving from the 1996 to the 1998 version. Examples

14   included the addition of numerous new defaults, standard dose-response models,

15   restrictions on the use of the No Observed Adverse Effects Level (NOAEL)

16   approach, and fixation on the 10% excess for a point of departure.

17

18   c)   **Sensitive subpopulations**: EPA should include a discussion of sensitive

19   subpopulations for all agents to which the general public (as opposed to healthy

20   workers) is exposed. Specifically, this discussion should include consideration of

21   pregnant females, the fetus, young children and adolescents, the ill, and the elderly.

22   The basis for the uncertainty factor or alternative modeling procedure used to

23   account for susceptibility of the young should be clearly stated. EPA should also

24   discuss other known or likely sensitive populations due to susceptibility factors *in*

25   *addition to* young age: nutritional deficits, preexisting disease, ethnicity, gender,

26   pregnancy – which may occur simultaneously (in combination) in various subsets of

27   the population.

28

29   In addition, the Agency should conduct systematic reviews to explore quantitatively

30   the extent of variability among individuals in the human population. In doing so the

31   Agency should consider modeling approaches, as well as comparisons of risks

32   across populations. Although not addressed in this review, we wish to endorse the

33

1   Agency's plan to hold a meeting later this year on GLs issues related to children – a
2   most sensitive subpopulation.
3

4   d)   **Background and multiple exposures**: EPA should discuss the need for the risk
5   assessment to consider background exposures/processes and concurrent exposures
6   with which the chemical (mixture) of interest may display additivity or interact
7   multiplicatively.
8

9   e)   **Guidance on the use of biologically-based models**: The 1998 draft does not
10   provide greater guidance than the 1996 GLs regarding the use of biologically based
11   DR models. No clear example has been provided of DR models "that would be
12   relied upon for low dose extrapolation." (SAB, 1997, p. 23) As in the 1997 report,
13   we continue to support the view that "if no such model can presently be identified,
14   a statement to that effect would be helpful."
15

16   f)   ~~**Severity of effect factor**: When the NOAEL approach is used to derive an Margin~~
17   ~~of Exposure (MOE) under these GLs (or if the LED$_{10}$ approach is used without the~~
18   ~~steepness factor), the approach is essentially the same as that for non-cancer effects.~~
19   ~~However, the severity of the effects being addressed may vary widely (from cancer~~
20   ~~mortality to subtle sub-clinical effects). Although this issue was not discussed at~~
21   ~~the public meeting, the Subcommittee believes it would be reasonable for EPA to~~
22   ~~account for severity of the health effect under consideration. For cancer this could~~
23   ~~be accomplished by explicitly including a factor to account for the severity of the~~
24   ~~cancer endpoint. This factor could be different for different types of cancer. If this~~
25   ~~approach is adopted, EPA could extend the procedure to similarly account for~~
26   ~~relative severity of different non-cancer health effects.~~
27

28   Other, more specifically focused findings directly addressing the Charge are:
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30

31   a)   There was agreement by the current Subcommittee that the revised GLs were a
32   significant improvement over the earlier version. In particular, the majority of the
33   Subcommittee strongly supports the proposed "Framework" as a means for

1   providing a working model for incorporating and interpreting data in a clear and
2   transparent manner. This model was developed as part of a World Health
3   Organization working group to deal specifically with large differences between the
4   approaches various countries were using to evaluate the same data with respect to
5   the risks posed by a given chemical (WHO, 19XX).
6

7   b)   There was a majority position that the narrative descriptor "known to be
8   carcinogenic to humans" or "known human carcinogen" should be retained. The
9   Subcommittee did not agree on whether to restrict use of this category to scenarios
10   in which there was conclusive epidemiological data. The majority of Members
11   favored this more restrictive approach believing that this position represents the
12   most reasonable interpretation of the phrase "known to be carcinogenic in humans."
13

14   c)   The use of a narrative is a key component of the hazard identification section.
15   Flexibility in how the hazard narrative is written is laudable, but a common format is
16   essential. All of the relevant data should be included.
17

18   d)   EPA should continue efforts to achieve compatibility with international
19   organizations such as the International Agency for Research on Cancer, the World
20   Health Organization, and European regulatory bodies
21

22   e)   The current guidance allows for departure from the linear default when supported
23   by mode of action information in favor of a non-linear or combined linear/non-linear
24   approach. The Subcommittee recommended that specific criteria for judging the
25   adequacy of data on a mode of action are needed and that specific examples should
26   be included to illustrate the application of these criteria.
27

28   f)   The proposed GLs document remains (perhaps necessarily) vague about what
29   specific data are required to reject defaults assumptions. Some additional
30   clarification on this issue is needed. The three examples provided help the reader to
31   understand this issue. Providing additional examples should further advance
32   understanding of the specific data required to reject defaults in the assessment step.
33   The Subcommittee recognizes that the Agency does not want to be prescriptive, as

4

1   the science will continue to evolve.

2

3   g)   The GLs should require specific, challenging testing of the proposed hypothesis
4   before rejecting the default assumption. The proposed assessment framework
5   appears to have sufficient flexibility to accommodate these developments.

6

7   h)   As part of the GLs' conclusions, there should be guidance on whether the data on
8   mode of action support, either strongly or moderately, a linear or non-linear
9   extrapolation of risk, or whether the data are inconclusive and that the linear default
10   should be used. Some Members expressed their strongly held view that the GLs
11   should require a much higher threshold of evidence for departure from defaults than
12   the "more likely than not" level currently found in the GLs, although most of the
13   Subcommittee accepted the Agency's position.

14

15   i)   To standardize the calculations, facilitate comparisons across chemicals, and
16   provide more clarity to the risk manager, the SAB recommended in 1997 that a
17   single risk level (e.g., 10%) be selected as the point of departure for (low dose)
18   non-linear extrapolation. The draft GLs now propose a value of 10%, while noting
19   that, in some situations (e.g., large experiments), it may be preferable to use a non-
20   standard value. In the current Agency proposal, it is noted that a lower point for
21   linear extrapolation can be used for tumor incidence study of "greater than usual
22   sensitivity." This is a reasonable approach, and one that the Subcommittee
23   endorses.

24

25   j)   In the case of Margin of Exposure (MOE) analysis, the Subcommittee continues to
26   be concerned about the linkage between the selected risk level and the
27   incorporation of adjustment and uncertainty factors. Use of a risk level less (or
28   greater) than 10% should, other things being equal, require a smaller (or larger)
29   uncertainty factor. The Agency is encouraged to develop explicit guidance
30   regarding the selection of uncertainty factors or MOE GLs for points of departure
31   other than 10%. Also, because of this problem, the Agency should strive to use the
32   standard point of departure whenever possible.

33

1   k)   There is continuing confusion about the relationship between the LED_{10}, or ED_{10}
2   and the NOAEL. The GLs should seek to clarify, not reinforce this confusion. In
3   addition, the new GLs propose two new ten-fold adjustment factors to be applied in
4   specific situations. Some Subcommittee Members questioned whether the need for,
5   or the magnitude of, these new uncertainty factors is sufficiently justified in the
6   GLs. Other Members supported the basic direction laid out in the draft GLs, but
7   noted that some further refinements were needed.
8

1   # 2. INTRODUCTION

2

3   **2.1 Background**

4

5   In September 1986, EPA published Guidelines for Carcinogen Risk Assessment (GLs) (51

6   Federal Register 33992-34003). Since that time, significant gains have been made in

7   understanding the carcinogenic process. Concurrently, the Agency's experience with the 1986 GLs

8   has revealed several limitations in their approach to cancer risk assessment. In April 1996, EPA

9   proposed revisions to the 1986 GLs (61 Federal Register 17960-18011). These revisions were the

10   result of a number of EPA-sponsored meetings, e.g., a 1994 peer review workshop (EPA, 1994),

11   recommendations contained in the National Academy of Sciences report (NAS, 1994) S*cience and*

12   *Judgment in Risk Assessment*, the U.S. Commission on Risk Assessment and Risk Management in

13   Regulatory Decision Making (GPO, 1997), and extensive EPA and Federal reviews.

14

15   The intent of the revised (GLs) is to take into account the available knowledge about the

16   carcinogenic process and to provide flexibility for additional changes in the future to more

17   realistically assess data, recognizing that the GLs cannot always anticipate future research findings.

18   Compared to the 1986 GLs, the revised 1998 GLs are intended to emphasize more complete

19   evaluation of all relevant information and to provide more guidance on the use of information on

20   the way an agent produces cancer (mode of action). Further, the revised GLs will be structured on

21   an analytical framework that recognizes a variety of conditions under which the cancer hazard may

22   be expressed (e.g., route or magnitude of exposure to the agent). The revised GLs promote the

23   evaluation of data related to mode of action as the first step. If the available data support a linear

24   relationship at low dose or if no clear alternatives exist, then a linear low dose extrapolation will be

25   utilized.

26

27   It should be noted that the SAB and SAP have been involved with risk assessment GLs,

28   including those for cancer, for many years. In 1986, the SAB/SAP conducted a review of the GLs

29   as proposed at that time [Will cite the SAB report.]. The Board has continually encouraged the

30   Agency to update all of its GLs in order to reflect the continuing advances of science. In 1992

31   (will check date) the Executive Committee of the SAB conducted a Consultation with the Agency

32   on the GLs and their future evolution [**will cite SAB Consultation**]. In 1997, the SAB's

1   Environmental Health Committee (EHC), augmented with representation from the Scientific

2   Advisory Panel (SAP), reviewed a draft of the revised GLs as they existed at that time (SAB,

3   1997). Although generally applauding the efforts of the Agency to update its GLs in keeping with

4   new scientific information and commentaries by authoritative groups (e.g., the

5   Presidential/Congressional Commission Report on Risk Assessment and Risk Management (US

6   GPO, 1997), the Board identified a number of areas where further improvements/clarifications

7   could be made - hazard descriptors, the use of mode of action information, and dose response

8   (DR) analysis (SAB. 1997). Revisions have been developed for these areas in response to these

9   comments and discussions within the Agency and it is these revised sections of the GLs that the

10   SAB Subcommittee reviewed at a meeting held in Washington, DC, on January 20-21, 1999 and

11   addresses in this report.

12

13   **2.2 Charge**

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15   The Charge addressed three major areas noted above, and within these areas, posed

16   specific questions. The elements of the Charge are:

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18   a)   Hazard Descriptors

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20   1)   Do the proposed narrative summaries and the five hazard descriptors

21   provide an appropriate and adequate basis for characterizing the technical

22   evaluation of carcinogenic potential?

23   2)   Is the guidance supplied for each of the proposed hazard descriptors

24   sufficiently clear and complete?

25

26   b)   Use of Mode of Action Information

27

28   1)   Is the guidance provided in the revised Sections 2.3.5 - 2.5 clear and

29   transparent?

30   2)   Please comment on the proposed key elements and their use in supporting a

31   mode of action conclusion via the framework (section 2.5).

32

33

1   3)   Are the case studies useful as illustrations of the guidance and framework?

2

3   c)   Dose Response Analysis

4

5   1)   Defining a Point of Departure: Please comment on the soundness of the
6   scientific rationale provided for the standard approach and options for
7   selecting departure points.

8

9   2)   Please comment on the adequacy and clarity of the guidance on this subject.

10

11   3)   Margin of Exposure Analysis: Please comment on the adequacy and clarity
12   of the guidance regarding how to perform a MOE analysis.   Are the
13   proposed approach and the factors for consideration in determining the
14   appropriate magnitude of the MOE appropriate? Specifically address the
15   use of factors to account for:
16   i)   the nature of the response (i.e., tumors or key events selected as the
17   point of departure for extrapolation)
18   ii)   steepness of the DR curve
19   iii) human intraspecies variability, including susceptible populations
20   iv)   interspecies variability.

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1   # 3 DETAILED FINDINGS

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3   **3.1 Hazard Descriptors**

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5   **3.1.1 Narrative Summaries and the Five Hazard Descriptors**

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7   The 1997 SAB review (SAB, 1997) of the 1996 draft Cancer Risk Assessment Guidelines

8   (GLs) (EPA, 1996) endorsed the (at the time, new) emphasis on the use of narrative discussion to

9   describe the weight of evidence (WOE). However, the reviewers found problems with its

10   implementation, particularly in the use of multiple terms (i.e., categories, descriptors, and sub-

11   descriptors). Given the complexities involved, the Committee could not come to a consensus as to

12   how this problem should be addressed. Some Members suggested eliminating categories in favor

13   of a narrative with selections made from the proposed thirteen sub-descriptors. Other Members

14   proposed use of the eight descriptors proposed by Ashby *et al.*, (1990) .

15

16   Questions posed by the Agency for this review addressed the adequacy of the proposed

17   narrative summaries and the five hazard descriptors in providing an appropriate and adequate basis

18   for characterizing the technical evaluation of carcinogenic potential, and the clarity and

19   completeness of the guidance supplied for each of the proposed hazard descriptors.

20

21   In its 1998 GLs document (EPA, 1998), EPA responded to the SAB and public comments

22   with a revised system of narratives and descriptors, incorporating five categories:

23

24   a)   *known to be carcinogenic to humans*

25

26   b)   *likely to be carcinogenic to humans*

27

28   *c)*   *suggestive evidence of carcinogenicity, but not sufficient to assess human*

29   *carcinogenic potential*

30

31   d)   *inadequate data for an assessment of human carcinogenic potential*

1   e)   *not likely to be carcinogenic to humans*

2

3   At the current Subcommittee's public meeting, there was considerable discussion of

4   alternatives to the EPA's proposed term "Known to be Carcinogenic to Humans." Suggested

5   options included:

6

7   a)   Restricting use of the descriptor "*Known to be Carcinogenic to Humans*" to those

8   agents for which conclusive epidemiologic data exists.

9

10   b)   Substituting "*Carcinogenic* to Humans"or "*known/as if known* to be carcinogenic

11   to humans" for" *known to be carcinogenic to humans."*

12

13   c)   Retaining the term, clarifying that the epidemiological evidence, while not

14   necessarily conclusive, should be substantially positive and. ~~accorded relatively high~~

15   ~~weight, especially when~~ supported by mechanistic data of known relevance

16

17   As with the 1997 SAB review, the Subcommittee did not reach a full consensus on this

18   issue at the 1998 public meeting. **There was however, a majority position, that the descriptor**

19   **"known to be carcinogenic to humans" or "known human carcinogen" should be retained.**[3]

20   The Members did not agree on whether to restrict use of this category to scenarios in which there

21   was conclusive epidemiological data. ~~The majority of~~ Most Members favored this more restrictive

22   approach believing that this position represents the most reasonable interpretation of the phrase

23   "known to be carcinogenic in humans." Consequently, to base assignment to this category upon

24   non-human data could be misleading, particularly to the general public.

25

---

[3]The reader will note that, throughout the body of this report, the terms "consensus," "a majority,"
"most," "some," "several," and the singular "Member" are used to denote the degree of support within the
Subcommittee for a given finding or observation. As listed above, these terms denote a decreasing level of support
within the Subcommittee for a given position, ranging from full agreement to a position held by one Member.
These adjectival assignments are based on a combination of positions taken (or comments made) at the public
meeting, and comments provided by the Subcommittee Members during the report preparation process. They do
not represent the results of a formal vote or count.

1   However, a minority of some Members recommended that, even with less than sufficient

2   epidemiologic data, an agent with strong animal evidence plus evidence (in exposed humans) that

3   the chemical is causing measurable changes that are on the causal pathway to cancer in humans,

4   should be considered to be carcinogenic to humans. This latter approach is consistent with the

5   findings of the National Toxicology Program (NTP, 1998) and the International Agency for

6   Research on Cancer's (IARC, 1994)) scheme which includes under the heading "the Agent

7   (mixture) is carcinogenic to humans" language stating that "...a chemical (mixture) for which the

8   evidence in humans is less than sufficient but for which there is sufficient evidence of

9   carcinogenicity in experimental animals and strong evidence in exposed humans that the agent

10   (mixture) acts through a relevant mechanism of carcinogenicity." It was suggested that in such a

11   case, EPA qualify the necessary epidemiologic evidence to be "a moderate amount of evidence

12   from human studies to suggest carcinogenicity, although it is not considered definitive." There

13   should be strong evidence linking the key event(s) known or likely to be related to carcinogenicity

14   in animals with the event(s) observed in humans exposed to the agent in question. The text should

15   stipulate that all four of the criteria listed in the draft GLs (section 2.6.2 p.2) (EPA, 1997) be met.

16

17   Also, as a general comment, the Subcommittee noted that the ultimate choice of categories

18   must be accurate, clear, and transparent in title and content if the document and the EPA are to

19   retain trust of the scientific and general population.

20

21   In summary, the Subcommittee's recommendations on each of the five proposed

22   classifications follow below. These recommendations are intended to express the underlying

23   rationale for each category, rather than prescriptive guidance on exact wording) are:

24

25   a)   **Known human carcinogen.** Use of this descriptor is appropriate when there is

26   convincing evidence from studies in humans demonstrating causality between

27   human exposure and cancer. Although, as noted above, this was the majority

28   position, theThe Subcommittee discussed recognized that there might be other

29   situations and circumstances that could lead to placement in this category (e.g., as

30   proposed by the IARC (1994) and NTP (1998), when there is strong animal

1   evidence [plus evidence in exposed humans]) that the substance causes measurable

2   changes in the causal pathway to cancer in humans), but did not reach any other

3   specific conclusions or consensus on this topic.

4

5   b)   **Likely to be carcinogenic to humans**. Typically, findings based on human data

6   that are generally supportive of carcinogenicity but of insufficient strength or

7   consistency to be definitive, or strong animal data, support assignment to this

8   category. This descriptor is appropriate for use when there is either limited

9   epidemiological evidence or ~~and~~ strong evidence from animal studies. This

10   categorization might also be used if the limited human and~~evidence and the limited~~

11   animal evidence is buttressed by findings~~evidence~~ that the carcinogenesis is

12   mediated by a mechanism that also operates in humans. It should also include

13   definitive animal data in the absence of definitive data establishing mechanistic

14   relevance. Some Members felt that strong mechanistic and structure activity data in

15   the absence of epidemiological evidence are sufficient to place an agent in this

16   category (This position is consistent with that taken by the Agency for some dioxin

17   and PCB congeners, as well as IARC's (1991) position on Benzedrine-based dyes.)

18   Another Member suggested that this category needs a clear statement regarding

19   exposure conditions under which this scenario is possibly true.

20

21   c)   **Suggestive evidence of human carcinogenicity**. This category encompasses cases

22   in which there is ~~limited or~~ mixed evidence of carcinogenicity in humans or animals,

23   or suggestive mechanistic data, but for which the data are insufficient to conclude

24   there is a likely causal relationship between exposure and cancer~~, and evidence of~~

25   ~~carcinogenicity in animals~~.

26

27   d)   **Inadequate data for an assessment of human carcinogenic potential**. This

28   classification should be used when there is a paucity of pertinent data on which to

29   base a judgment.

30

1   The Subcommittee recommends that the concept expressed by the term "conflicting
2   data" be narrowed by replacing it with "irreconcilable data" (e.g., a significant
3   effect at one dose in one study, but negative responses at this dose and higher doses
4   in a replicate study that are statistically incompatible with the positive response seen
5   in the one study). Apparent inconsistencies in data may result from a number of
6   reasons including chance, differences in design, and the fact that complimentary
7   component(s) may not be present in all studies (Rothman (p. 18), 1986)

8

9   e)   **Not likely to be carcinogenic to humans**. The Subcommittee found the
10   supporting text for this category to be quite good, but has some recommendations.
11   Because agents in this category are unlikely to be tested further, the criteria for this
12   finding should be stringent (e.g., negative data from several rodent and non-rodent
13   studies incorporating relevant routes of exposure). The GLs text should state that
14   there must be strong evidence for finding a lack of effects in animals. Stringent test
15   requirements are needed to discount carcinogenicity by specific routes of exposure.
16   When using epidemiological data to support the finding, multiple studies should be
17   required~~, and upper limits on relative risk should fall below those levels supporting~~
18   ~~a causal association~~.

19

20   The GLs' text should also state that route specificity must be supported by a range
21   of other relevant data. Under the requirement for "evidence that carcinogenic
22   effects are not likely by a particular route of exposure," EPA should add words to
23   the effect that "This conclusion ~~and this~~is relevant only to this~~the only~~route of
24   exposure ~~route likely to be encountered~~."

25

26   **3.1.2 Clarity and Completeness of the Guidance**

27

28   The use of a narrative is a key component of the hazard identification section. Flexibility in
29   how the hazard narrative is written is laudable, and a common format is essential. All of the
30   relevant data should be included.

1   In developing the revised GLs, EPA should strive whenever possible, to achieve
2   compatibility with international organizations such as the IARC , the World Health Organization
3   and European regulatory bodies. Within that context, an emphasis should be placed on the factors
4   of weight of the evidence, conditions of exposure, and relevance to humans. The wording for the
5   descriptors is suggested above, with an emphasis on integrating all of the available data. Some
6   Members felt the a need to address the relevance of animal data to human risk at environmentally
7   relevant doses, while others held that this should occur in the risk characterization, but not at the
8   hazard identification stage. However, all Members agreed that this is an important consideration,
9   and the Subcommittee was in full agreement that the actual environmental concentration was an
10   essential factor to consider in assessing the potential carcinogenic *risk.* However, there was a
11   range of opinion on the question of whether and how anticipated environmental concentrations
12   should be factored in when describing the potential carcinogenic *hazard*.

13

14   Some Members felt that it did not make sense to label a substance as "carcinogenic" when
15   all anticipated exposures in the environment were well below that level at which a carcinogenic
16   mechanism might come into play; e.g., formation of stones, following by irritation that leads to a
17   carcinogenic response--but only at high doses. For these Members, the question being asked in the
18   Hazard Identification stage is: "Does this substance pose any carcinogenic risk at anticipated
19   environmental exposures?" Other Members felt that the concentration considerations are
20   appropriately reflected in the Exposure Assessment and in the Risk Characterization steps of the
21   risk assessment process. For these individuals, the Hazard Identification question is: "Does this
22   substance pose any carcinogenic risk under any possible exposure conditions imaginable?"

23

24   In the end, the determination of which question is being asked in the Hazard Identification
25   step is a really a policy decision. In either case, the Agency has an obligation to be very explicit
26   about which question it is asking. In addition, in order to be consistent and thereby enhance public
27   understanding of the risk assessment process, the question in the Hazard Identification stage for
28   cancer should be consistent with the question in the Hazard Identification stage for non-cancer
29   effects, such as reproductive effects. Also, these questions must be so posed that take into account
30   the fact that a biological response such as carcinogenicity or reproductive toxicity is a function of

1 both dose and exposure (rate and duration of exposure), as well as the genetic background of the

2 host.

3

4 **3.2 Mode of Action**

5

6   The 1996 EPA GLs proposal called for the use of mode of action (MOA) information to

7 guide both decisions about the human relevance of animal responses, and decisions on the conduct

8 of dose response (DR) assessment. Although the 1997 SAB EHC agreed in general about the

9 importance of mode of action data, some expressed concern that the 1996 GLs did not provide a

10 means of judging the sufficiency of the evidence to assess mode of action data. The current

11 guidance allows for departure from the linear default when supported by mode of action

12 information in favor of a non-linear or combined linear/non-linear approach. The Subcommittee

13 recommended that specific criteria for judging the adequacy of data on a mode of action are

14 needed and that specific examples should be included to illustrate the application of these criteria.

15

16   EPA believes that developing precise criteria for evaluating a mode of action is not

17 possible. Any attempt to do so would quickly become out of date and restrictive. Instead, the

18 Agency put forward a framework for evaluating a mode of action that is loosely adapted from the

19 considerations developed by Bradford Hill for judging causality in epidemiologic studies (Hill,

20 1965). The proposed approach was found to be acceptable by most, but not all, Members of the

21 Subcommittee. EPA's revised Sections 2.3.5 -2.5 of the 1996 GLs proposal (EPA, 1966, pp.

22 17977-17981) now include a framework for using mode of action information. Three case studies

23 were included in the draft GLs to illustrate the application of the framework to judge the adequacy

24 of available data to support a postulated mode of carcinogenic action. The case studies are

25 intended to be included in Appendix D of the final GLs.

26

27 **3.2.1 Clarity and Transparency of the Guidance**

28

29   When the revised GLs and public comments were reviewed in 1997, the SAB Committee

30 (SAB, 1997) requested that EPA provide additional guidance on evaluating "Mode of Action"

1 (MOA) data. There was general agreement by the current Subcommittee that the revised GLs

2 were a significant improvement over the earlier version. In particular, the majority of the

3 Subcommittee strongly supports the proposed "Framework" as a means for providing a working

4 model for incorporating and interpreting data in a clear and transparent manner. This model was

5 developed as part of a World Health Organization **(WHO, 19XX**) working group to deal

6 specifically with large differences between the approaches various countries were using to evaluate

7 the same data with respect to the risks posed by a given chemical. It was not meant to dictate final

8 interpretations, but rather to ensure that the available data are reviewed in a comprehensive manner

9 that. ~~It~~The model also draws on the use of the Bradford Hill criteria employed by epidemiologists

10 for many years (Hill, 1965). By applying this type of rationale to mechanistic data, one is forced to

11 look at such basic issues as identifying key events in the mode of action, examining the strength,

12 consistency and specificity of the associations between these key events and cancer, evaluating the

13 dose-response and temporal relationships of key events and cancer, determining the biological

14 plausibility and coherence of the data, and discussing alternative modes of action. Such a

15 framework will provide a clear path for data presentation that should be scientifically rigorous and

16 transparent.

17

18   While expressing this strong general support for this revised section of the GLs, the

19 Subcommittee also suggested revisions to strengthen the section, including:

20

21   a)   It was suggested during the public meeting that the question "*Do the key events*[4]

22   *suggest possible sensitive populations?*" be added to the mode of action section.

23   Furthermore, if data on humans, such as enzyme induction and disease are available

24   and indicate that they may place a subset of the population ~~be~~ at greater risk due to

25   age, gender, disease state etc., this finding should be addressed in relevant sections.

26   E.g., the variation in individual enzyme levels and disease states should be stated in

27   the hazard identification document.

---

[4] Subcommittee Members noted that the term "Key Event" is not the ideal designation for a process which is a biological continuum. In addition, the list for consideration for evaluation of data on "key events" as provided in the proposal needs to be prioritized. The first point should address the presence of a direct or indirect effect on DNA; also, the time course "bullets" need to be combined.

1   b)   EPA should add a statement noting that lack of strength, consistency, specificity of
2   association or dose-response weakens the mode of action. As presently written, the
3   document focuses only on those factors that strengthens the association. It was
4   also pointed out that the WOE derived from such associations should not just be a
5   statistical evaluation. Rather, it ~~is~~ should be a thorough evaluation of the data that
6   identifies coherent, versus flimsy data sets. For example, WOE statements should
7   be worded in the context of whether the hypothesis associating a mode of action
8   with a carcinogenic response has survived~~stood up to~~ multiple experimental
9   challenges. I.e., that there is a consistent association under a variety of conditions.
10

11 c)   The proposed GLs document remains (perhaps necessarily) vague about what
12   specific data are required to reject defaults. Some additional clarification on this
13   issue is needed. The three examples provided help the reader to understand this
14   issue. Providing additional examples should further advance understanding of the
15   specific data required to reject defaults in the assessment step. The Subcommittee
16   recognizes that the Agency does not want to be prescriptive, as the science will
17   continue to evolve. The GLs should require a thorough evaluation and specific,
18   challenging testing of the proposed hypothesis before rejecting the default. The
19   framework appears to have sufficient flexibility to accommodate these
20   developments.
21

22 d)   As part of the GLs' conclusions, there should be a statement ~~for instance,~~ about
23   whether the data on mode of action support either (strongly or moderately) a linear
24   or non-linear extrapolation of risk, or whether the data are inconclusive and that the
25   linear default should be used. Some Members expressed their strongly held view
26   that the GLs should require a much higher threshold of evidence for departure from
27   defaults than the "more likely than not" level currently found in the GLs, although
28   most of the Subcommittee accepted the Agency's position.
29
30

1   **3.2.2 Proposed Key Elements and the Framework**

2

3   Previous versions of the EPA GLs recognized the importance of mechanism of action and

4   the need to include this type of information in the WOE analysis. Such considerations were not a

5   major factor in the actual decision making phase of the assessment process. The 1996 GLs not

6   only reversed this approach but gives mode of action a central role in the cancer risk assessment

7   process. In the April, 1996, version of the GLs, the mode of action section included a listing of the

8   uncertainties and factors that need to be considered in any cancer risk assessment, and folded

9   these factors into a WOE approach. The current revision improves significantly the earlier GLs

10   version by providing a specific framework which includes a new "Bradford Hill" (Hill, 1965) type

11   of evaluation.

12

13   However, the most important part of this framework is its focus on identifying the key or

14   critical elements in the carcinogenic process. This is a significant refocusing for the GLs. The

15   outcome could be further improved if, in addition to identifying the critical elements, the process

16   would identify which of these elements are rate-determining or rate-limiting, enabling a focus on

17   the important steps of the risk determination, rather than on a multitude of factors as is now the

18   case with the WOE evaluation. Although we can set absolute limits for dose and time, the mode

19   of action approach can be used to establish actual dose thresholds. Exposures not exceeding the

20   dose and time thresholds are not toxic. and, as some argue, may even be beneficial (hormesis)

21   NAS/NRC, 1990). We can use toxicokinetics to identify the risk limiting processes associated

22   with metabolism of the agent and toxicodynamics to do the same for the effects or injury. For

23   agents with a long half-life (such as mirex, dioxins, asbestos, etc.), the toxicokinetic processes are

24   more likely to be rate determining/limiting than the toxicodynamic processes. Conversely, for

25   agents with a short half-life (such as benzene and most other solvents), the toxicodynamic

26   processes are more likely to be rate determining/limiting. The Agency should follow closely work

27   in progress by two National Research Council/National Academy of Science Subcommittees

28   (NAS/NRC, in preparation) to develop a mathematical approach for dealing with these issues. A

29   mathematical approach for dealing with these issues has been developed by Rozman (in

30   preparation) for two National Research Council/National Academy of Science Subcommittees

1   (Subcommittee on Acute Exposure Guideline Levels (in preparation) and the Subcommittee on
2   Strategies to Protect the Health of Deployed U.S. Forces, Task 2.1 (in preparation)). His
3   approach extends the toxicologic principles in Haber's Law and can be used to identify realistic
4   worst case situations. It might be quite informative to compare the margin of exposure (MOE)
5   obtained by the approach developed by Rozman's (ct=k divided by ct^x=k) with that of the current
6   GLs (LED or benchmark divided by actual exposure situation).
7
8   One final concern emphasized during the public meeting is the need for the Agency to
9   include an evaluation of cancer risks to sensitive subpopulations (such as children pregnant
10 women, young females, the aged, specific disease states etc.). Since the mode of action section is
11 one place to address this issue, further revision of this section to incorporate these factors may be
12 appropriate. There was also some discussion of the need to provide a characterization of how the
13 Agency might use human data in this process. This information~~finding~~ should also be folded into
14 the MOA section. These issues pose important, but difficult problems. The Subcommittee is
15 concerned that attempts to rework the present document to include these areas may result in a
16 significant further delay. If it appears that these problems cannot be resolved expeditiously,
17 perhaps the best solution would be to provide some wording in the MOA section indicating that
18 guidance on the use of MOA data would follow as the susceptible population and human data
19 evaluation procedures were developed; and concurrently, publish the current product as a final
20 document, but one explicitly recognizing the need for future updating. (see section 4.0).
21
22 **3.2.3 Case Studies**
23
24   The three case examples addressing mode of action present two overarching concepts.
25 First, the case examples are meant to present three different modes of action: a) thyroid
26 tumor/thyroid hormone interaction; b) bladder tumor/urinary calculi interaction; and c) stomach
27 tumor/direct irritation interaction. Second, the cases are meant to present different levels of
28 scientific support, i.e., a) from a complete, rich data set; b) to one with adequate, but not complete
29 data; and c) to one with insufficient data. Each case example meets these requirements, and each
30

1   is organized in accordance with the GLs. At least one Subcommittee Member believed that the

2   cases would be more valuable if the actual agent was identified.

3

4   The Subcommittee believes that adding specific information on the relevance of mode of

5   action to humans to the three case examples would improve them. In each case example, it would

6   be useful to mention the relevance of the particular mode of action to population subgroups,

7   especially children and child-bearing women. Some Members felt that, in each case example, it

8   would be useful to include a statement about the potential levels of human environmental

9   exposures, compared to exposure levels used in animal studies; other Members, however, felt that

10 such information should be taken into account at later stages in the risk assessment process after

11 the Hazard Identification stage.

12

13   As part of the conclusions, it would be useful for the GLs document to point out specific

14 limitations of the data in each case. In particular, identification of the data gaps that are *critical* to

15 the risk assessment should be identified.

16

17 **3.3 Dose-Response Analysis**

18

19   **3.3.1 Defining a Point of Departure**

20

21   The 1996 draft GLs employed a "point of departure" dose level to mark the beginning of

22 low dose extrapolation. The lower 95% confidence bound on the 10% effect level for tumor (or

23 precursor response) incidence (LED_{10}) was proposed as the standard point of departure in order

24 to be consistent with approach taken in the proposed benchmark approach for non-cancer

25 endpoints (EPA, 1997).

26

27   The Agency specifically requested the Subcommittee's comments on the selection of the

28 LED_{10} as the point of departure. In its previous review (SAB, 1997), the SAB voiced a number of

29 preferences that included a lower limit as well as central estimates (ED_{10}) and standard versus

30 case-by-case choice of response level (1.0% to 50%). The 1997 SAB review concluded that the

1 approach to determining the point of departure should be harmonized for non-linear carcinogens

2 and the benchmark methodology for non-carcinogens. The SAB also recommended that a single

3 risk level be utilized, e.g., the point estimate of the $ED_{10,}$ when the low dose non-linear approach is

4 applied; and that both the point estimate as well as upper and lower confidence bounds should

5 routinely be reported.

6

7   The present draft GLs proposes to retain the use of the LED_{10} as the standard point of

8 departure, but the revised text contains an expanded discussion of the standard approach and

9 options for the point of departure.

10

11 **3.3.1.1 Soundness of the Scientific Rationale**

12

13   The Agency's 1996 Proposed GLs for Cancer Risk Assessment employed a "point of

14 departure" as the starting point for low dose extrapolation. The selection of the point involves

15 selecting a DR model, selecting a risk value, and calculating statistical confidence bounds. In the

16 1997 review, the SAB advised the Agency to provide further specific guidance on these aspects of

17 the procedure and offered a number of suggestions. The Agency has been very responsive to the

18 advice and has thought through a number of difficult issues to develop the current proposal. We

19 understand that the Agency plans to make the overall procedure available on the World Wide Web

20 for public use, and the Subcommittee endorses this action and commends the Agency for this

21 initiative. Nonetheless, the Subcommittee has some remaining concerns about the definition of the

22 point of departure and the overall procedure.

23

24   To standardize the calculation, facilitate comparisons across chemicals, and provide more

25 clarity to the risk manager, the SAB recommended in 1997 that a single risk level (e.g., 10%) be

26 selected as the point of departure for (low dose) non-linear extrapolation. A value of 10% was

27 proposed, while noting that, in some situations (e.g., large experiments), it may be preferable to

28 use a non-standard value. In the current Agency proposal, a risk value of 10% has been selected

29 for (low dose) linear and non-linear applications, although it is noted that a lower point for linear

30

1 extrapolation can be used for tumor incidence study of "greater than usual sensitivity." This is a

2 reasonable approach, and one that the current review endorses.

3

4   The EPA's scientific rationale for selection of 10% for cancer endpoints is based on

5 findings for cancer and non-cancer endpoints. The draft GLs correctly note the work of Haseman

6 (1983) indicating that for typical cancer bioassays a 10% response is at or just below the limit of

7 sensitivity. Therefore, it is very important to be accurate about the strength of the scientific

8 evidence for selection of 10% for non-cancer health effects. However, the current draft GLs also

9 state that "Because the NOAEL in study protocols for non-tumor toxicity can range from about a

10 5% to a 30% effect level" (Faustman *et al.*, 1994) adopting the 10% effect level as the standard

11 point of departure will accommodate most of these data sets without departing from the range of

12 observation." (EPA, 1997). This statement needs to be corrected to reflect that the Allen *et al*.

13 and Faustman *et al*. papers (1994) evaluated only a few developmental toxicity endpoints and not

14 "non-tumor toxicity," in general.

15

16   As noted above, the use of 10% risk value as a point of departure may not be appropriate

17 in all situations. A lower point for linear extrapolation can be preferable for studies of greater than

18 usual sensitivity, and a higher point may be necessary to remain within the range of observation for

19 certain insensitive studies.

20

21   In the case of MOE analysis, the Subcommittee continues to be concerned about the

22 linkage between the selected risk level and the incorporation of adjustment and uncertainty factors.

23 Use of a risk level less (or greater) than 10% should, other things being equal, should require a

24 smaller (or larger) uncertainty factor. **The Agency is encouraged to develop explicit guidance**

25 **regarding the selection of uncertainty factors or MOE GLs for points of departure other**

26 **than 10%. Also, because of this problem, the Agency should strive to use the standard point**

27 **of departure whenever possible.**

28

29   The GLs should also note that the point of departure derived from the analysis of human

30 DR data may need to be lower than a 10% risk level. For example, one of the best known human

1   carcinogens -- cigarette smoke -- produces only a 10% level of lifetime risk of lung cancer in those

2   who smoke the most (**Ref Needed**).

3

4   Guidance on the use of NOAELs versus LED or ED values is ambiguous. Thus, the

5   Subcommittee continues to be concerned there may be unnecessary confusion and inconsistency in

6   the application of GLs. It is also concerned that a risk manager may improperly apply these

7   approaches without a clear understanding of how and why they differ. The argument that the

8   NOAEL approach is the most practicable way of proceeding with a mixed data base (of continuous

9   and quantal data) was not compelling. However, some Members felt that, until the Agency gains

10   more experience with the GL, it might be useful to encourage evaluation of both the NOAEL

11   approach and approaches that use more quantitative methods (e.g., the LED or ED). At present,

12   they felt that it may be premature for the Agency to develop a science policy default to use the

13   LED or ED value over the NOAEL. while there ~~There~~ is insufficient experience with application

14   of these quantitative approaches to cancer bioassays ~~and~~ but limited experience with other toxicity

15   studies. The quantitative methods (including decisions of whether LED vs ED should be used as

16   point of departure, or how to apply this approach to continuous data) are not sufficiently well-

17   established to support the LED/ED approach as the method of choice in all cases. In any event,

18   the proposed GLs should encourage a decision process driven by careful scientific evaluation,

19   rather than a default assumption that a mathematically calculated point of departure is

20   automatically more scientifically sound. In addition, the Subcommittee recommends that EPA

21   pursue a modeling approach for continuous data, together with efforts to gain a quantitative

22   understanding of the relationship between precursor data and tumor incidence.

23

24   There is continuing confusion about the relationship between the LED_{10}, or the point

25   estimate of the ED_{10} and the NOAEL. The GLs should seek to clarify, not reinforce this

26   confusion. The draft proposal indicates that the LED_{10} can be regarded as an improved and

27   harmonized estimate of the NOAEL (GLs Section 3, page 7, line 15). Statements such as this

28   contribute to the general misunderstanding of the relationship between these DR indices. To

29   facilitate an understanding of the quantitative relationship between the LED_{10} and the NOAEL, the

30

1 Agency is encouraged to compare them systematically across a wide range of cancer data sets, and

2 to make the results available to the public.

3

4

5   Under the draft proposal, the Agency will apply a standard curve-fitting procedure to

6 model the DR relationship and will make the procedure available to the public on the Agency's

7 Website. EPA should conduct a rigorous peer review of this procedure. The Agency also

8 expressed its intention to include procedures to identify situations where the standard procedure

9 fails. The Agency is commended for this effort, which is responsive to the 1997 SAB

10 recommendation that the Agency select a default procedure for use in calculating the point of

11 departure. The examples presented by the Agency at the January, 1999 public meeting incorporate

12 some of the specific model suggestions made by the EHC . n addition to the suggestion that

13 EPA's standard models be made available for peer review, several Members suggested that the

14 GLs provide more flexibility and allow consideration of other possible models, particularly for

15 epidemiological data.

16

17   As in the 1997 review, the current Subcommittee encourages the Agency to develop

18 specific guidance to address problematic data sets, such as those with poor fits, extreme curvature

19 or large intercurrent mortality. Another area needing guidance pertains to the modeling of dose

20 rate and age effects. Specific, detailed guidance could be developed separately from the more

21 general GLs, and following peer review, posted on the Agency's Website.

22

23   The current Draft GLs indicate that when time-to-tumor information is available, more

24 elaborate, time-dependent models, are appropriate. This is the case when mortality is sufficiently

25 high, but the use of time dependent models may not be necessary in most cases. Detailed guidance

26 on this should be developed, with new procedures and provided on the Agency's Website after an

27 appropriate level of external peer review. Another related issue, and one for which considerably

28 more guidance is needed, has to do with differences in time scale for the different species. This is a

29 particular concern when precursor data are used.

30

1   During the Subcommittee's meeting, there was a lively discussion on the use of confidence
2   bounds and point estimates in DR analysis. The 1998 draft GLs selected as the point of departure
3   for linear and non-linear approaches the LED_{10}, that is the lower 95% confidence limit on a dose
4   associated with a 10% excess risk – noting that the "use of the lower limit takes experimental
5   variability and sample size into account." The current draft GLs also state that the central estimate
6   (i.e., the point estimate of the ED_{10}) is appropriate in some situations, for example, in ranking
7   chemical potencies across chemicals. In addition, the GLs state that the point estimate of the ED_{10}
8   and upper and lower confidence limits will always be presented for reference.
9
10   The 1998 draft GLs, in essence, adopted the SAB's suggested guidance from its 1997
11   review (SAB, 1997), which stated:
12
13   *"The consensus of the Committee was that both point estimates and statistical bounds can*
14   *be useful in different circumstances, and recommended that the Agency routinely*
15   *calculate and present the point estimate of the ED_{10} and the corresponding upper and*
16   *lower 95% statistical bounds. It may be appropriate to emphasize point estimates in*
17   *activities that involve ranking agents as to their carcinogenic hazard. On the other hand,*
18   *it may be appropriate to emphasize lower statistical bounds in activities designed to*
19   *develop an appropriate human exposure value, since such activities require accounting*
20   *for various types of uncertainties and a lower statistical bound on the ED_{10} (LED_{10}) is a*
21   *scientifically-based approach for accounting for the uncertainty in the true value of the*
22   *ED_{10}."*
23
24   Although there was continued support for this position and the one taken by the Agency in
25   their draft GLs, there were some divergent views expressed during the 1999 review. One such
26   view held that using the lower confidence limit as the point of departure addressed uncertainty at
27   the wrong stage in the analysis, and that it would be more appropriately taken into account at a
28   later stage in the process, namely the reporting of a recommended MOE. Another Member noted
29   that if this viewpoint were to be adopted, the ratio of the point estimate of the ED_{10} to the LED_{10}
30   could be used to estimate an additional adjustment factor addressing the statistical uncertainty

1   associated with the point estimate of the ED_{10}. ~~be used to calculate the additional uncertainty~~

2   ~~factor required to address the instability and uncertainty associated with the ED_{10} point estimate.~~

3   ~~However, the ED_{10} point estimate is unstable, and is not an overall advance for the risk manager,~~

4   ~~who is likely to be confused by the concept that the estimate is precise and unbiased, but unstable~~

5   ~~and inaccurate~~ (Further discussion of this topic is located in section 3.3.1.2).

6

7   For linear extrapolation, the point of departure is expressed as a human equivalent dose,

8   including those scenarios where default interspecies scaling is applied. Under the MOE analysis,

9   the point of departure appears to be expressed in terms of the animal dose, with the default

10   adjustment factor accounting for differences in body size taken into account in developing the

11   default MOE. This inconsistency in the definition contributes to the over all confusion about what

12   the MOE factors represent.

13

14   As noted by the SAB in its 1997 review, there is considerable room for confusion and

15   misinterpretation by risk managers and the public about the use of the term "MOE,"especially how

16   it relates to terms like "margin of safety" or "margin of error." To address this issue, some

17   Members recommend that instead of, or in addition to, a MOE, the Agency report an advisory or

18   reference concentration for cancer endpoints.

19

20   The 1997 SAB review also noted the need for more guidance on DR analysis for human

21   data, particularly in the application of the new approach to DR analysis, and to locating the point

22   of departure. There may be insufficient time and resources to provide more detailed guidance in

23   this version of the GLs. If so, the Agency is encouraged to proceed to develop further detailed

24   guidance, through workshops and perhaps extramural research and development. Improved

25   procedures could be posted on the Agency Website as they are developed and peer reviewed.

26   Whenever a risk level other than 10% is used, the uncertainty and adjustment factors should be

27   modified accordingly.

28

29   **3.3.1.2 Adequacy and Clarity of the Guidance**

30

1   As noted above, the current draft GLs present the ED_{10} point estimate, and both upper and
2   lower confidence limits. They also propose the use of the statistical lower bound on the ED_{10} (the
3   LED_{10}) as a the point of departure for MOE analysis.

4

5   The presentation by EPA at the Subcommittee meeting outlined four main reasons for use
6   of the LED_{10} (rather than the point estimate of the ED_{10}) as the point of departure: a)
7   harmonization with non-cancer risk assessment; b) the LED_{10} rewards better experimentation (e.g.
8   larger sample size); c) the LED_{10} is stable to changes in experimental design (e.g. group size), and
9   d) the LED_{10} takes into account uncertainty in the experimental data. Each of these points are
10   discussed in detail below.

11

12   a)   **Harmonization**: It was pointed out by some Members that harmonization between
13   cancer and non-cancer endpoints could be achieved by using the central estimate for
14   both endpoints. When EPA sought expert advice about whether to use the central
15   estimate or the lower confidence estimate on the dose for non-cancer endpoints, the
16   majority of the expert peer consultants at the EPA Benchmark Dose Peer
17   Consultation Workshop (conducted by the International Life Sciences Institute)
18   (Barnes, 1995) recommended that the central estimate should be used. Others
19   disagreed, noting previous benchmark dose-analyses seen by the EHC used the
20   LED_{10} as the point of departure, and EPA does not seem to have adopted the
21   central estimate for non-cancer endpoints.

22

23   b)   **Rewards better experimental design**: Although the LED_{10} theoretically rewards
24   better experimentation, it may have little practical effect in many cases. For
25   example, the effect of doubling the number of animals in each dose group increases
26   the LED_{10} by only 20-35%, and the gains appear to be minimal. In any event, most
27   bioassays for carcinogenicity are conducted according to ~~and~~ FIFRA/TSCA test
28   rules and ~~(although not applicable to all studies, especially mechanistic studies~~
29   ~~performed to support an MOE approach)~~ must~~should~~ meet standards calling for
30   minimal use of animals to be acceptable to the Agency. It should be noted that not

1   all studies, especially mechanistic studies, are performed according to specified

2   guidelines. In these cases, the LED-based approach may provide incentives to

3   conduct studies with greater statistical power. It is important to consider the

4   impact on study designs resulting from an ED- versus LED- based approach.; i.e.,

5   the potential incentives for small insensitive studies and disincentives for more

6   powerful studies under the ED-based approach.

7

8   c)   **Stability of the LED$_{10}$**: The Subcommittee generally agreed with EPA's position

9   that use of the LED$_{10}$ provides a ~~more stable~~ measure with lower variance than does

10   the ED$_{10}$. On the other hand, the ED$_{10}$ is, by ~~statistical~~ definition, the best estimate

11   of the target dose.

12

13   d)   **Accounting for experimental uncertainty**: The MOE guidance provided by the

14   EPA involves application of several factors that account for various types of

15   uncertainties. The Subcommittee agreed that the uncertainty in the experimental

16   data should be taken into account, and most Members thought that the use of the

17   LED$_{10}$ is a scientifically sound method for accomplishing this goal.

18

19   The Subcommittee discussed other factors regarding the use of the ED$_{10}$ as the point of

20   departure:

21

22   a)   ~~**The ED$_{10}$ provides greater accuracy**~~**The variability of the point estimate of the**

23   **ED10 versus the LED$_{10}$:** The point estimate of the ED$_{10}$ is ~~the best~~an unbiased

24   estimate of the dose that causes an increased risk of 10%, although the variance of

25   this estimate is often relatively large. The ~~objective of the ED$_{10}$ is to identify a dose~~

26   ~~with an increased risk equal to 0.10 (10%) whereas the objective of the~~ LED$_{10}$

27   (95% statistical lower bound of the ED$_{10}$) generally is less variable than the point

28   estimate~~to identify a dose with an increased risk of at most 0.10 (10%). In other~~

29   ~~words, the objective of the ED$_{10}$ is to be equal to the target dose, whereas the~~

30   ~~objective of the LED$_{10}$ is to be below the target dose.~~

1

2   b)   **The ED_{10} provides for clearer exposition:** Some Members found that the

3   meaning, calculation, and communication of the ED_{10} concept to be more

4   straightforward for an ED_{10} point estimate than for LED_{10}. Therefore, the point

5   estimate of the ED_{10} is likely to be more readily interpreted by risk managers and by

6   the public. Other Members felt that this introduced difficulties later in the process

7   because the rationale for using the ratio of the point estimate of the ED_{10} to the

8   LED_{10} ~~ratio~~ will be difficult to communicate to risk managers.

9

10   In summary, the Subcommittee still supports presenting the point estimate of the ED_{10}

11   along with both lower (LED_{10}) and upper (UED_{10}) bounds as called for in the Agency draft. The

12   Subcommittee also supports the use of the ED_{10} as the primary statistic for relative hazard/potency

13   ranking, although statistical confidence bounds on the ED_{10} (both the LED_{10} and the UED_{10}) could

14   be used to evaluate the uncertainty in the rankings. There were differences of opinion within the

15   Subcommittee regarding the use of the LED_{10} for the point of departure. Some Members believed

16   strongly that use of the point estimate of the ED_{10} was preferable, but others (equally strongly)

17   preferred use of the LED_{10}.. These latter Members suggested that, as a compromise, the ED_{10} be

18   used as the point of departure, and that the ED_{10} /LED_{10} ratio be incorporated as an index which

19   could be used to develop an Reference Concentration (RfC). This alternative approach would

20   provide exactly the same advisory exposure level as would the approach proposed in the draft

21   GLs. If an RfC or Reference Dose (RfD) was derived, concern over the use of an ED_{10} would be

22   lessened; also, some felt that this alternative approach is more transparent, and would treat the

23   uncertainty in the experimental data in a manner that is more consistent with how other

24   uncertainties are handled.

25

26   **3.3.2 Margin of Exposure Analysis**

27

28   The 1996 proposed GLs called for the use of a margin-of-exposure (MOE) analysis as a

29   default dose-response procedure. This approach was to be used when there is sufficient evidence to

30   support a non-linear mode of action at low doses (in those cases when available data are inadequate

1   for development of a biologically based DR (BBDR) model. The MOE is the ratio of the point of

2   departure (e.g., the LED_{10}) to the dose associated with the environmental exposure(s) of interest.

3   The purpose of the MOE analysis is to provide information on how much reduction in risk may be

4   associated with a given target exposure level so that a risk manager can make a determination of the

5   adequacy of a given MOE.

6

7   The 1997 SAB Committee felt that there might be confusion and misinterpretation of the

8   concept and recommended additional guidance and examples of the MOE approach be provided in

9   the GLs. The 1998 draft GLs treatment of this issue (section 3.1.3 of the revised text) includes

10   expanded guidance on how to perform a MOE analysis and is intended to replace section 3.1.2 of

11   the 1996 proposal . Three case studies are included (in the draft GLs' Appendix E) to illustrate how

12   to perform a MOE analysis. However, concern was expressed that the risk manager may be less

13   inclined to use the advisory MOE than the RfC, and in the end the uncertainty index (the ratio of

14   point estimate of the ED_{10} to to the LED_{10} ratio) may not be used.

15

16   The Agency asked the Subcommittee to comment on the clarity of the GLs' guidance, as

17   well asaddresing a) nature of the response; b) steepness of the DR curve; c) the proposed use of

18   data from key events; and d) inter-species variability. In addition to the four factors identified by

19   the Agency, the Subcommittee has identified two other factors that should be considered, as well,

20   comprising: e) .human intraspecies variability, including susceptible populations; and f) comments

21   on mode of action. The Subcommittee's responses follow below in sections 3.3.2.1 and 3.3.2.2.

22

23   **3.3.2.1 Adequacy and Clarity of the Guidance**

24

25   The current draft contains several examples illustrating MOE analysis. The Subcommittee

26   commends the Agency for preparing these examples. They provide very useful insight into how the

27   Agency would apply the GLs.

28

29   When it first became known that the Agency was adopting new GLs that would permit the

30   wider use of scientific data in risk assessment, it was generally assumed that these GLs would allow

1   some of the assumptions, including the adjustment and uncertainty factors used in the 1986 GLs, to

2   be replaced by factors or procedures derived from scientific data. However, as it has turned out,

3   most of the assumptions and factors present in the old GLs are still present in the new GLs (One

4   exception to this is the use of pharmacokinetic data in the new GLs for making animal to human

5   extrapolations). In addition, the new GLs propose two new ten-fold factors, one to account for the

6   slope of the DR in the observable range and the other to account for limitations in amount and

7   quality of precursor data. Some Subcommittee Members questioned whether the need for, or the

8   magnitude, of these new uncertainty factors is sufficiently justified in the GLs. Other Members

9   supported the basic direction laid out in the draft GLs, but noted that some further refinements were

10 needed. A majority of the Subcommittee questioned the rationale for the new safety factors.

11

12 **3.3.2.2 Critical Factors in Margin of Exposure Analysis**

13

14   The major factors are:

15

16 a)   **Nature of the Response**: Some Members felt that the proposed MOE approach

17   does not use the existing direct data on tumor incidence well. It may not use the

18   tumor incidence data at all (i.e., it may use"key event" incidence/measurements

19   instead), or it may use the tumor data somewhat to define a LED_{10} for animals, but

20   then proceeds with a whole series of assumptions whose applicability and accuracy

21   are often unknown when developing a level that might be considered to be

22   sufficiently protective for humans. In cases where there is little information about

23   the adjustment factors (key events, steep/shallow slope, interspecies extrapolation,

24   or heterogeneity in sensitivity), some Members felt that the MOE procedure is

25   overly conservative. Others noted a number of additional factors that should be

26   addressed to if one wishes to proceed from a dose causing a 10% cancer incidence in

27   animals to one that could be considered safe for a heterogenous human population.

28   These other factors include background exposures of agents functioning via the

29   same mechanism; inter-individual variability; adjustments for differences in body size

30   of animals versus that of humans; and severity of endpoint. For example, in the

1 GLs' Appendix E, Example 1, even though there were no significant findings of liver

2 cancer below the highest dose, the MOE extrapolation advocated a dose 3,000-fold

3 lower. Given that the EPA's policy aim is to be conservative with regard to health

4 protection, the multiplication of layers of conservative factors can conceivably

5 produce an overly conservative result.

6

7 An aim of the GL's MOE approach is to provide a method to estimate safe doses for

8 non-linear modes of carcinogenic action that will more firmly rooted in scientific

9 data than a linear model. Some believe that such an approach would yield a less

10 conservative result than does the linear approach, but there is no measure of how

11 much less conservative it actually is when applied with defaults. Again, examining

12 Example 1 in Appendix E of the draft GLs, a rough calculation shows that the

13 estimate generated using the MOE approach may be nearly as conservative as a

14 produced by application of a linear model. Specifically, applying the derived MOE

15 dose-reduction factor of 3,000 to a linear curve produces an estimate of risk of

16 $\sim 10^{-5}$, which is not dissimilar to a level one would choose using the linear

17 extrapolation procedure. Without further specifics on the mode of action discussed

18 in the example, it is not possible to determine whether or not the MOE approach is

19 appropriate.

20

21 b) **Steepness of the Dose Response Curve** (also affecting the severity of the

22 endpoint): The GLs introduce a new adjustment factor of 10 to be applied to the

23 point estimate of the ED_{10} (except in exceptional cases when the observed DR slope

24 at the LED_{10} is very large; this will be discussed in more detail below). This factor

25 would not be applied if the DR were "steep enough" at the point of departure.

26 Specifically, it is proposed that a 10-fold default factor be applied if the slope of the

27 estimated dose- response curve at the point of departure is less than a factor of three

28 steeper than a straight line drawn from the point of departure to the origin. This

29 approach assumes that an observed slope will continue into the low dose range;

30 consequently, this adjustment is intended to account for differences in observed

1   slope. Although not stated explicitly in the revised GLs document, EPA scientists at
2   the review meeting confirmed that the steepness of the slope would be evaluated
3   using the lower bound DR curve defining the LED_{10}, rather than on the best estimate
4   of the DR curve that defines the point estimate of the ED_{10}.

5

6   Although the specified approach implies that this new adjustment factor would not
7   be applied to very steep DRs, it appears that the conditions necessary to exclude use
8   of the uncertainty factor are so severe that its use would be required in almost all
9   cases. The steepness/shallowness of the dose-response curve at the LED_{10} appears
10   to be largely a function of the power (k) of the polynomial dose-response curve that
11   is selected, which, in turn, is largely driven by the spacing of doses in experiments if
12   only the highest dose shows an increase in incidence. Insofar as the GLs' Appendix
13   E (Example 1 and Example 2) are fairly typical, one is likely to find that a value of
14   three for k provides an adequate fit for many/most of the animal data sets in which
15   only the highest dose shows any tumor effect (or "key event" effect), and the MOE
16   procedure will therefore dictate an additional factor of 10. If one looks at the actual
17   data presented in these examples, one sees that, at the two lower doses in both
18   examples, the incidence does not differ significantly from controls, even though in
19   one case, the incidence in the mid-dose group is double that of the controls. The
20   lack of steepness of the dose-response curve is likely to be primarily an artifact of
21   the experimental design (namely, the spacing of doses) and the sparseness of the
22   data.

23

24   Some Members felt that if there is any applicability of the concept of shallow/steep
25   slope, it would be in the case where there is some evidence of elevation at one or
26   more doses below the highest dose, yet a linear curve does not fit the data well
27   (although one would suspect this will seldom occur; a linear curve will frequently fit
28   in such situations given the usual sparseness of the incidence data). There may also
29   be continuous data where the linear fit is poor. Some Members also felt that the
30   shallow/steep slope operational definition needs a major reformulation. If the

1   adjustment factor for shallow/steep slope is to be used, it should be reserved for the

2   cases where there is actual evidence for a shallow slope (e.g., with two or more

3   elevated data points) and should not be applied when only the highest dose shows an

4   elevation, since the inference of a shallow slope in such cases may be largely an

5   artifact of the spacing of the doses, and is not based on any actual evidence of a

6   shallow slope (i.e., the next-to-highest dose point is already down to baseline).

7   Some other Members emphasized the importance of some procedure for moving to a

8   point below that of 10% risk was needed and any changes to the current proposals

9   should address this issue.

10

11   The reason given by the Agency for this new uncertainty factor is to "Lower the

12   dose from the LED_{10} to approach a zero to 1% effect level (or from a LOAEL to

13   NOAEL)." Some Members found this an appropriate motivation for an additional

14   factor; others did not. Here the GLs appear to be equating LED_{10} with a LOAEL,

15   despite the fact that the LED_{10} was characterized earlier as "an improved and

16   harmonized estimate of the NOAEL," and despite data relied upon by the Agency

17   indicating that the LED_{10} is, on average, less than the NOAEL already. One way to

18   interpret this is that the EPA considers the traditional use of the NOAEL to not be

19   protective enough, at least for severe endpoints such as cancer. The Agency is now

20   moving to the use of a measure (the LED_{10}) that, based on currently available

21   information, appears to be generally more protective than the NOAEL, and it is also

22   adding a new 10-fold adjustment factor.

23

24   The addition of this new adjustment factor raised a number of concerns with many

25   Members of the Subcommittee. For them, the reasons given for incorporating the

26   new factor in the GLs' assessment were not convincing. First of all, the LED_{10} is

27   already generally lower than a NOAEL, so adding an adjustment factor to lower the

28   dose from a LOAEL to a NOAEL was not thought to be appropriate. Others

29   strongly disagreed, noting the importance of reducing exposure below a level

30   producing a 10% cancer incidence. Second, since the factor is arbitrary; why should

1   one stop at 1% risk? Speaking rhetorically, why not divide by 100 and reduce the

2   dose from the LED_{10} to one approaching a zero to 0.1% risk? Third, although the

3   rationale for the new adjustment factor may not be conceptually related to cancer, it

4   is apparently being proposed only for cancer. Some found this to be at odds with

5   the earlier recommendation by the Subcommittee that approaches for cancer and

6   non-cancer be harmonized to the extent possible Some Members noted, however,

7   that the EHC, in its 1997 report (SAB, 1997), stated that harmonization does not

8   necessarily mean the adoption of the same factors. Furthermore, it may point out a

9   problem in the framework for RfC derivation from severe non-cancer endpoints.

10 Fourth, the use of this new adjustment factor is apparently limited to cases in which

11 the LED_{10} is used as the departure point, and would not be applied to the NOAEL.

12 Some Members felt that this introduces an intolerable incompatibility between the

13 two approaches. Since the LED_{10} is already (in general) lower than a NOAEL, this

14 approach means that assessments that employ the LED_{10} will generally be at least

15 10-fold more conservative than assessments that employ the NOAEL. **(redline text**

16 **above inadvertently deleted by the editor when revising the previous draft**)On

17 the other hand, some Members felt that the NOAEL should not be used without any

18 adjustment factor.

19

20 **(NB--Text below eliminated as repetitive of material in preceding para (b))**

21 ~~The GLs introduce a mechanism whereby this factor would not be applied if the DR~~

22 ~~were "steep enough" at the point of departure. Specifically, it is proposed that a 10-~~

23 ~~fold default factor be applied if the slope of the estimated dose- response curve at~~

24 ~~the point of departure is less than a factor of three steeper than a straight line drawn~~

25 ~~from the point of departure to the origin. This approach assumes that an observed~~

26 ~~slope will continue into the low dose range; consequently, and that this adjustment is~~

27 ~~intended to account for differences in observed slope. Although not stated explicitly~~

28 ~~in the Draft GLs document, EPA scientists at the review meeting confirmed that the~~

29 ~~steepness of the slope would be evaluated using the lower bound DR curve defining~~

30 ~~the LED_{10}, rather than on the best estimate of the DR curve that defines the ED_{10}.~~

1   The specific proposed adjustment introduces a "bright line" decision point based

2   upon arbitrary criteria, as there is no specific rationale for either the factor of three

3   for differences in slopes nor the 10-fold adjustment factor. Also, as noted above, the

4   measured slope can be highly influenced by both the experimental design (dose

5   spacing) and the selected DR model, so its reliability is questionable. This latter

6   point is well-illustrated by the example presented in the draft GLs' revised Appendix

7   E (EPA, 1998). According to the reported analysis, the slope at the LED_{10} was

8   0.37, the slope from the LED_{10} to the origin was 0.15, and since $0.37/0.15 = 2.5 < 3$,

9   an additional factor of 10 was required. However, when the model is modified to

10 include a fourth degree term, the fit is even better. Furthermore, with this model, the

11 slope at the LED_{10} is 0.46, and the slope from the LED_{10}, the origin is 0.12. Since

12 $0.46/0.12 = 3.8 > 3$, according to this modeling, no additional factor of 10 is

13 warranted. (These calculations are based on the best estimate curve and were made

14 before it became known that EPA intends to employ the curve defining the LED_{10}

15 rather than the point estimate of the ED_{10}.) This illustrates that this three-fold slope

16 ratio rule is likely to be highly model dependent and, consequently, unreliable. Some

17 Subcommittee Members were also concerned that the use of the curve defining the

18 LED_{10}, rather than the best-estimate curve defining the point estimate of the ED_{10}, is

19 not justified. These Members felt that the best-estimate curve should be used so that

20 the focus is on the biological DR curve instead of a curve defining the statistical

21 uncertainty of the biological response.

22

23 It is instructive to compare the result of the example in Appendix E (EPA, 1998)) to

24 what would have been obtained if the NOAEL approach has been applied. The

25 NOAEL in this case is 0.65 mg/kg/d, which by chance is also the value of the LED_{10}

26 obtained by EPA. However, if the NOAEL were used as the take-off point, no

27 additional factor of 10 for steepness of slope would be applied. This, therefore,

28 illustrates the imbalance in the currently proposed approach of allowing either the

29 NOAEL or the LED_{10} to be used as the point of departure. But again, some

30

1   Members found this to be appropriate because of the severity of the endpoint, and

2   that the use of the NOAEL would require an additional adjustment factor.

3

4   In order to avoid the "bright line" decision regarding whether or not to ~~the~~ use the

5   ten-fold adjustment factor, ~~no factor of ten, an alternative would be to~~ one could

6   apply a factor equal to 10*[slope from the point estimate of the ED10 to

7   origin]/[slope at the ED_{10}]. Although this approach (supported by several Members

8   of the Subcommittee) suffers from most of the same shortcomings as that currently

9   proposed (arbitrariness and model dependency), it would at least provide a sliding

10   scale that would avoid "bright line" decision rule of the proposed approach.

11

12   In addition to the new 10-fold uncertainty factor that is added for steepness of slope

13   (per the criteria noted above), ~~if the LED_{10} is used,~~ EPA also proposes that an

14   additional 10-fold uncertainty factor to be applied automatically when the NOAEL

15   for a key event is used as the point of departure (section 3.1.3.2, pg. 12, lines 14-17,

16   EPA, 1998). There is no clear scientific rationale provided for this additional 10-

17   fold factor, and the criterion for its removal ("...when the full array of data sets

18   supports a conclusion that the NOAEL is probably a no effect level or very close.")

19   (ibid) is not sufficiently defined in the GLs document provided to the Subcommittee.

20   However, EPA staff provided one rationale for using this 10-fold factor at the SAB

21   meeting. The NOAELs in a large number of developmental toxicity studies were

22   found to be approximately equivalent to the calculated LED_{10}. Since EPA's stated

23   goal (EPA, 1998, pg. 13) is to lower the dose to approach a 1% effect level as a

24   point of departure for cancer EPA felt that it is necessary to use an additional 10x

25   uncertainty factor. If this is an accurate reflection of EPA's rationale, then EPA

26   essentially regards the traditional NOAEL as a LOAEL and believes that additional

27   10x uncertainty factor should be added to reach a "true" NOAEL. EPA is

28   essentially stating that the current practice of using the NOAEL plus default 100-

29   fold uncertainty factor has not been sufficiently protective, and that 1000-fold should

30   now be the default uncertainty factor. Some Members felt that there is no scientific

1   evidence to support this position and, if this position is adopted the Agency they

2   should make very clear that it is a policy decision, based on added concern posed by

3   the cancer endpoint, i.e., a value-driven decision, not a science-driven decision, but

4   remaining consistent with the Administration's 1995 risk characterization policy.

5   Other Members found this approach to be supported by data and justified, noting

6   that an adjustment to go from a dose associated with a 10% incidence of health

7   effect to one with a minimal level of effect was needed. These Members questioned

8   why a similar factor was not applied for other chronic endpoints, particularly when

9   the effect observed is severe.

10

11   In summary, many Members of the Subcommittee believe that the rationale

12   presented for this new adjustment factor is weak, and questioned whether this new

13   adjustment factor is justified. Other Members agreed with the rationale but thought

14   further work on the method is desirable. If the Agency decides to retain some

15   curvature factor, the specific approach to be applied needs to be reworked.

16

17   c)   **The Proposed use of Data from Key Events**: For carcinogen GLs, defining risk

18   based on evidence of actual ~~malignant~~ tumor induction (rather than on putative, but

19   perhaps poorly correlated, key events) is a solid bottom line and should not be

20   abandoned without strong justification. Incorporating the shape of the

21   dose-response of "key events" is consistent with the objective of incorporating more

22   science, particularly mechanistic data related to mode of action. However, reliance

23   on one or more early events, that may be necessary but not sufficient for causation,

24   can lead to incorrect inferences about the shape (and steepness) of the dose-response

25   curve in the low-dose region. Nevertheless, one could make the case that key events

26   that are fairly proximal to the tumor induction step in tumor pathogenesis have some

27   biological plausibility as events to consider. On the other hand, use of those events

28   that are further removed and earlier in the possible chain of pathogenetic events,

29   becomes questionable. The early events are likely to have a poor correlation with

30   tumor induction, suffering especially from lack of specificity, i.e., many "false

1   positives." If key events are to be used quantitatively, there should be much fuller

2   specification and justification of events to be considered "key."

3

4   The shape of the dose-response relationships depends on the dose-dependence of all

5   component events in the multistage process and not just a single event -- even an

6   early event. One key event might be linear with respect to dose and another key

7   event might be non-linear or even have a threshold. Hence one event being linear

8   does not imply that the whole process is linear. However, non -linearity of one event

9   does imply that the whole process is non-linear, although the dose-response may be

10   linear in the low dose range. Each "event" is a process and the overall sum of events

11   is not first order." Furthermore, an earlier event may be associated with a steeper

12   slope and be reversible. Thus, the shapes of the dose-response relationships of all

13   known necessary and sufficient key events and the dose-response of the tumor

14   incidence must be jointly considered.

15

16   The proposed adjustment factor of 10 to account for difference in dose between the

17   occurrence of the key event and the observation of tumors was not sufficiently

18   justified in the GLs. Some Members questioned the existence of data indicating that

19   a factor is needed at all, while others noted this addressed, in part, the contributions

20   of background exposures. Some questioned the magnitude of the factor, and

21   whether it was a policy-driven decision, or one based on the available science. The

22   Subcommittee recommends that the data available be studied and used to inform this

23   decision.

24

25   d)   **Inter-species Variability**: If the point of departure is calculated as a "human

26   equivalent dose" determined from a body weight scaling factor (such as interspecies

27   equivalence on a (body weight)$^{3/4}$ basis), then no additional factor should be

28   included for animal-to-human extrapolation. The proposed 3-fold factor is

29   (incorrectly, to some Members) justified as corresponding to toxicodynamic species

30   differences, as if the (body weight)$^{3/4}$ scaling from animal dose to human equivalent

1   dose only accounted for toxicokinetic differences. Some Members argued that the

2   (body weight)$^{3/4}$ scaling from animal dose to human equivalent dose includes both

3   toxicokinetic and toxicodynamic differences. For example, in the paper by Travis

4   and White (1988) which contributed to the adoption of (body weight)$^{3/4}$ scaling

5   from animal dose to human equivalent dose, the interspecies equivalence refers to

6   the interspecies differences in maximum tolerated dose, and maximum tolerated dose

7   reflects both toxicokinetics and toxicodynamics. An alternative viewpoint is that

8   toxicodynamics for carcinogenesis and for the acute endpoints studied by Travis and

9   White differ sufficiently, and that, in the case of cancer, interspecies differences in

10 toxicodynamics will be greater. Recent research by Rhomberg and associates

11 provides further evidences of differences for acute versus chronic endpoints

12 (Rhomberg, 1996. It should also be noted that subsequent analyses of the data used

13 by Travis and White (ibid) pointed out the possibilities of significant underestimation

14 of risk in certain cases when 3/4 scaling is used (Watanabe *et al.*,

15 1992).

16

17 e)   **Human intraspecies variability, including susceptible populations:**

18   Heterogeneity in susceptibility among humans is clearly an appropriate factor for

19   consideration ~~to take into account~~ by the GLs. The Subcommittee recognizes the

20   importance of inter-individual variability and the need to consider the range among

21   individuals in the population, rather than focusing on the comparisons of one large

22   population group (e.g., males, females, children, adults) with another. It is quite

23   difficult to determine (epidemiologically) how the most sensitive members of a large

24   variable population differ from the average. Recent work with biomarkers may

25   eventually provide better means of characterizing the range of variability (~~Rothman~~

26   ~~et al., 1986~~Perera, 1997). Unfortunately, with regard to carcinogenesis there are

27   relatively few systematic data of good quality that shed light on this issue, although

28   data are emerging to explore further this issue. The research area that has perhaps

29   the most extensive human data on susceptibility factors is radiation carcinogenesis.

30   With regard to ionizing radiation and carcinogenesis by gender, there are (if we

1   ignore the obvious differences -- breast, ovarian, uterine, prostate cancers), modest

2   differences between sexes at other sites, such that females are at slightly higher risk

3   than males, although the differences are nearly all less than two-fold. With regard to

4   age at radiation exposure, children are at increased risk compared to adults, but the

5   factor is only about two- to four-fold, and certainly not as much as 10-fold more

6   than the average for all ages. (NAS/NRC, 1990; ICRP, 1991) There are two cases

7   where there are strong radiation age effects, namely for thyroid and breast cancer.

8   For breast cancer the increased sensitivity at young ages is less than 10 times the

9   average for all ages, but the increased sensitivity may be on the order of 10-fold for

10   thyroid cancer (because thyroid cancer risk drops to virtually zero for irradiation

11   after age 30). For childhood cancer risk following in utero exposure, the risk is

12   probably several times as great as when irradiation occurs in childhood (although the

13   evidence regarding this is mixed), but the two groups seem to have similar

14   radiogenic cancer risks in adulthood.

15

16   With regard to genetic factors and radiation, there are very few human data. The

17   most extensive study, that of persons who received radiotherapy for bilateral

18   retinoblastoma (homozygous mutation of the Rb gene), showed about a 5-fold

19   greater radiation risk for cancer induction than expected (Wong, 1997). However,

20   this risk was largely limited to a few uncommon types of cancer, especially

21   sarcomas, and did not include the common cancer types (breast, lung, colon, etc.) At

22   the present time, radiation risk with regard to a number of other hereditary mutations

23   has not been defined, e.g., for BRCA1/2, APC, HNPCC. There is some evidence

24   that hereditary p53 mutations (Li-Fraumeni syndrome) may confer added radiation

25   risk, but the data ~~are not very consistent or~~ have not been systematically evaluated

26   (Malkin *et al.,*, 1992; Strong, 1993). There are also two controversial studies

27   suggesting increased radiation risk for breast cancer in those with the ATM

28   **(MEANING OF ATM, PLS–is it ataxia-telangiectasia mutation? SAM)**

29   mutation (Swift *et al.*, 1991; Athma, *et al.,* 1996). If the ATM-radiation risk is real,

30   it is probably 2- to 5-fold.

1   Thus, the evidence from radiation epidemiology suggests that a 10-fold factor for
2   susceptibility would be a health-conservative factor, although a caveat should be
3   added that radiation does not require any metabolic processes for its carcinogenic
4   action, so it may not be representative of some chemical carcinogens .
5
6   Key factors that explain variability in human disease risk are age, socioeconomic
7   status, smoking, gender, routes of exposure, nutritional factors, and genetic factors.
8   Because cancer causation is multi factorial and there are both protective attributes as
9   well as risk factors in the same individual, population overall variability may be less
10   extreme than variability on a single factor might suggest. The distribution of risk
11   among subpopulations studied for the disease of interest can be informative in the
12   assessment of human variability. For example, lung cancer risk among
13   subpopulations that differ according to factors such as diet, ethnicity and gender
14   vary by about two-six fold. The highest risk group for lung cancer, male smokers,
15   have a 10-fold higher risk for lung cancer than non-smokers. It is rare for an
16   epidemiology study to identify risks greater than six when comparing
17   subpopulations. Interactive effects have been observed in rare circumstances.
18   Furthermore, methods exist to define a point of departure in the presence of
19   interacting agents. Some Members felt that a careful analysis of all relevant
20   information should precede a decision to apply a default factor to account for human
21   variability; other Members found it imperative to apply a factor to account for
22   human variability in the absence of more definitive information. Flexibility should
23   exist to use uncertainty factors other than 10 (or higher or lower than 10), should
24   scientific data exist to support some other value.
25
26   Frequently, experimental data are available on male and female animals of different
27   species, and the risk assessment is based on the most sensitive species and sex.
28   Consequently, some variations in risk across populations, such as between males and
29   females, may already be accounted for and may not require an additional uncertainty
30   factor, or the full value of a default factor. It also should be noted that a 10- fold

43

1   range between most- and least- sensitive individuals might generally be accounted

2   for by a factor nearer to three than to 10, because the departure point is presumed to

3   apply to the average individual rather than to the least sensitive. However, research

4   on variability suggests the existence of ranges considerable greater than this for

5   specific chemical carcinogens (e.g., benzene [Rothman *et al*., 1997] and 4-

6   aminobiphenyl [Bois *et al.,* 1995]).

7

8   The Subcommittee Members recommended that the EPA evaluate the data on

9   chemical carcinogens and make a more scientific determination of an appropriate

10   uncertainty factor for protecting more sensitive individuals. The Subcommittee also

11   recommends that any such review be conducted as a peer-review so that a credible

12   and balanced evaluation is produced.

13

14   f)   **Comments on Mode of Action:** The GLs call for the use of a margin-of-exposure

15   (MOE) analysis when there is sufficient evidence to support a non-linear mode of

16   action. A procedure modeled after the Hill causality criteria for epidemiological

17   studies (Hill, 1965) has been provided to assist in determining MOE. Whereas these

18   criteria are useful, it needs to be clearly recognized that they only provide a means of

19   determining whether the MOA of a chemical is sufficiently well understood. They

20   are not designed to determine whether the mode of action is linear or non-linear at

21   low doses. The GLs include the use of a margin of exposure approach as a new

22   default procedure to accommodate cases in which there is sufficient evidence of a

23   nonlinear dose-response, but not enough evidence to construct a mathematical

24   model for the relationship. ~~The GLs state that a default assumption of non-linearity~~

25   ~~is appropriate when the chemical is non-mutagenic and there is sufficient MOA~~

26   ~~evidence to indicate that the response is non-linear, i.e., falls off more quickly than~~

27   ~~linear.~~ However in the examples, the focus appears to be on determination, first,

28   that a MOA is reasonably well understood qualitatively and second, that it is an

29   indirect mode of action. The question of whether the dose-response is linear or non-

30   linear is ignored. It appears to be an unstated assumption that an indirect mechanism

1 will be non-linear. ~~This assumption is highly questionable. For example, Connolly~~

2 ~~and Andersen (1991) caution against assuming that dioxin-induced cancer has a~~

3 ~~non-linear DR solely because it occurs through binding with receptors.~~ This issue is

4 key to the non-linear approach and must be addressed in the GLs. Linearity is a very

5 specific type of dose-response, and the hypothesis that a DR is linear can be tested

6 within the observable range using standard statistical tests. ~~It would seem that such~~

7 ~~test should play a role in the evaluation of the evidence of whether a dose-response~~

8 ~~is linear.~~

9

10 As noted in the 1997 EHC report the terms 'linear' and 'non-linear' as used in the GL

11 can lead to some misunderstanding and confusion. Many well-studied agents

12 associated with a DNA reactive mode of action are observed to have non-linear dose

13 response relationships (e.g., vinyl chloride, diethylnitrosamine). Non-linear tumor

14 dose response relationships due to increased mortality in high dose groups and dose

15 dependent pharmacokinetics are frequently observed. Alternative terminology could

16 be employed to address this problem is. e.g., the use of "linear at low doses" and

17 "non-linear at low doses;" "low dose linear" and 'low dose non-linear;" or

18 "non-threshold' and 'presumed threshold-like."

19

20 Although not addressed in detail at the Subcommittee's review meeting, we wish to

21 point out that the issue of background additivity is also overlooked in the GLs. In

22 cases when there is considerable exposure to exogenous and endogenous chemicals

23 operating by similar mechanisms, the DR in the population can be linear even if the

24 DR from zero exposure to higher doses is significantly non-linear.

25

4. CONCLUSIONS AND COMMENTS

1
2
3   The Agency stated that the current draft of the GLs is intended to provide greater flexibility
4 to the risk assessor, so that new scientific data can be used, when they exist, in place of traditional
5 defaults. While the draft, in being responsive to the SAB's 1997 request for more definition and
6 explanation in some areas, certainly moves in the direction of greater flexibility, some flexibility has
7 actually been lost; e.g., the incorporation of several new defaults, standardization of dose-response
8 models, restrictions on the use of the NOAEL approach, and a decision to use the LED_{10} as a point
9 of departure. The current version demonstrates, however, the Agency's progress and commitment
10 to implementing the recommendation of the Risk Commission (NAS/NRC, 1994) to harmonize GLs
11 for cancer and non-cancer risk assessment.

12

13   Given the above findings, the Subcommittee wishes to make a major recommendation to the
14 Agency. **We believe strongly that these GLs should become operative, as soon as judiciously**
15 **possible.** The old GLs have been around for more than a decade; the Agency has been working on
16 the revised GLs since 1990, including sponsoring several public workshops on GLs issues; and the
17 SAB has had a Consultation and two reviews -- with at least one more in the offing to address GLs
18 issues related to children. Clearly, there are GLs issues noted in this report that need to be
19 addressed and/or re-visited, continually (and new ones which will arise). However, it is important
20 to consolidate the progress that has been made in the current document, and have it officially issued
21 at the earliest possible date.

22

23   In summary, the Subcommittee is aware of the difficulty that the Agency faces in trying to
24 'titrate' just the right amount of flexibility into the GLs. In point of fact, however, the issue cannot
25 be settled *a priori.* The Agency should continually consider the matter as the GLs move into
26 common practice and experience demonstrates how the flexibility should be adjusted. Therefore,
27 we encourage the usage of the GLs and that the Agency gain valuable experience with them as soon
28 as judiciously possible.

29
30

1   The above accomplishments, and the preceding detailed discussion notwithstanding, the

2   Subcommittee wished to highlight for the Agency several additional issues (both within, and

3   without, the scope of the Charge).[5] These issues are:

4

5   a)   **Primacy of public health protection:** The Subcommittee believes that it is essential

6   that, as noted in the previous review (SAB. 1997, p.18) the GLs state at the outset

7   that "the primary goal of EPA actions is public health protection and that,

8   accordingly, as an Agency policy, the defaults used in the absence of scientific data

9   to the contrary should be health protective." These defaults should be clearly

10   explained in the revised GLs text, including the assumptions of low dose linearity

11   and the relevance of animal data to humans. The basis for the various default

12   uncertainty factors should also be clearly described.

13

14   ~~The general reservations and concerns expressed in the 1997 SAB review remain.~~

15   ~~That review noted that such statements in the 1996 draft GLs conveyed the general~~

16   ~~message that the GLs are public health conservative Because this impression is likely~~

17   ~~to be incorporated into guidance and work products transmitted to the risk manager~~

18   ~~and the public, it deserves greater scrutiny.~~

19

20   b)   **Lost flexibility:** Some Members expressed concerns that EPA, in responding to the

21   SAB's request for more definition in several areas, actually reduced, rather than

22   increased, flexibility in moving from the 1996 to the 1998 version of the GLs. They

23   cited several examples, including the reliance on the LED_{10} as a point of departure,

24   the addition of numerous new defaults, standard dose-response models, and

25   restrictions on the use of the NOAEL approach. ~~and fixation on the 10% excess for~~

26   ~~a point of departure.~~

27

28

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[5] In addition, detailed comments from individual Members of the Subcommittee are provided in Appendix A.

1	c)	**Sensitive subpopulations**: EPA should include a discussion of sensitive
2		subpopulations for all agents to which the general public (as opposed to healthy
3		workers) is exposed. Specifically, this discussion should include consideration of
4		pregnant females, the fetus, young children and adolescents, the ill, and the elderly.
5		There should be a summary of existing data (including biomarker data),
6		acknowledgment of gaps in knowledge, and a discussion of the factors that make or
7		may place the population at increased or decreased risk to this agent. Differences
8		between the young and adults in metabolic pathways, DNA repair, cell proliferation,
9		immune surveillance or other critical or important processes that may alter
10		susceptibility, as well as cancer risk, should be addressed to the extent that data are
11		available on how these biomarkers translate into population risk. The basis for the
12		uncertainty factor or alternative modeling procedure used to account for
13		susceptibility of the young should be clearly stated. EPA should also discuss other
14		known or likely sensitive populations due to susceptibility factors *in addition to*
15		young age: nutritional deficits, preexisting disease, ethnicity, gender, pregnancy –
16		which may occur simultaneously (in combination) in various subsets of the
17		population (see Perera, 1997). It should also be noted that interindividual individual
18		differences in enzyme activities etc., do not necessarily imply similar changes in
19		cancer susceptibility because they are not the rate limiting step.
20		
21		The Agency should conduct systematic reviews to explore quantitatively the extent
22		of variability among individuals in the human population. In doing so the Agency
23		should consider modeling approaches, as well as comparisons of risks across
24		populations. In performing such comparisons, it is noted that (typically) average risk
25		serves as the basis of comparisons, and that such comparisons may substantially
26		underestimate the variability among individuals in populations. For certain
27		applications, such as the MOE approach, it is particularly important that variability
28		not be significantly underestimated.
29		
30		

48

1   d)   **Consideration of background and multiple exposures**: EPA should discuss the

2   need for the risk assessment to consider background exposures/processes and

3   concurrent exposures with which the agent (mixture) of interest may display

4   additivity or inhibition, or interact multiplicatively.

5

6   e)   **Guidance on the use of biologically-based models**: The 1998 draft does not

7   provide greater guidance than the 1996 GLs regarding the use of biologically based

8   DR models. No clear example has been provided of DR models "that would be

9   relied upon for low dose extrapolation." (SAB, 1997, p. 23) As in the 1997 report ,

10   we continue to support the view that "if no such model can presently be identified, a

11   statement to that effect would be helpful."

12

13 f)   The preceding technical discussions notwithstanding (sections 3.3.2.2 (b)), the

14   ultimate answer to the question of whether or not to include a special adjustment

15   factor because the endpoint under discussion is cancer, is not actually a scientific

16   question, but a policy decision.

17 **NB–text below deleted and moved to the Appendix (sub para. (r))**

18 f)   ~~**Using a severity of effect factor**: When the NOAEL approach is used to derive an~~

19   ~~MOE under these GLs (or if the LED$_{10}$ approach is used without the steepness~~

20   ~~factor), the approach is essentially the same as that for non-cancer effects.~~

21   ~~However, the severity of the effects being addressed may vary widely (from cancer~~

22   ~~mortality to subtle sub-clinical effects). The Subcommittee believe it would be~~

23   ~~reasonable for EPA to account for severity of the health effect under consideration.~~

24   ~~E.g., for cancer this could be accomplished by explicitly including a factor to~~

25   ~~account for the severity of the cancer endpoint. This factor could be different for~~

26   ~~different types of cancer (e.g., non-melanoma skin cancer versus pleural~~

27   ~~mesothelioma). If this approach is adopted, it is recommended that the Agency~~

28   ~~extend the procedure to similarly account for relative severity of different non-cancer~~

29   ~~health effects.~~

30

1   APPENDIX A–DETAILED COMMENTS FROM INDIVIDUAL

2   SUBCOMMITTEE MEMBERS

3

4   The following comments from individuals on the Panel are offered to the Agency for its

5   information. They do not represent a Subcommittee consensus position on any point, but they are worthy

6   of further consideration as these GLs continue to evolve. The Subcommittee does not expect the Agency

7   to address these comments in its response to this report.

8

9   a)   One reviewer found the argument in the thyroid dose example to be internally

10   inconsistent, especially regarding rodent sensitivity, given the findings in the dog.

11   For that example, it is recommended that values based on the LED_{10} approach be

12   presented. There is no good rationale for using the NOAEL over the LED_{10} in this

13   example.

14

15   b)   It was clear from the Subcommittee discussion on mode of action at the meeting that

16   the EPA GLs will be used as a blueprint for testing by chemical manufacturers.

17   They must therefore be rigorous and specific as to the types of data to be

18   considered. It is important to explicitly include the following types of data:

19

20   1)   Are there parallel data in humans (e.g.; in the thyroid case, on liver enzyme

21   induction and Thyroid Stimulating Hormone)? Gaps in knowledge should be

22   noted.

23   2)   Data available on populations known or likely to be sensitive to the chemical

24   alone or in combination with other chemicals (e.g., children, people with

25   preexisting thyroid disorders etc.) should be discussed.

26   3)   Discuss whether background exposures/processes occur in the human

27   population.

28   4)   Data on interactions known, or likely to occur, between the chemical of

29   interest and other exposures should be provided.

30   5)   Gaps in testing and scientific knowledge should be identified..

1   6)   Are the IARC (1991) criteria for species-specificity or qualitative differences

2   between species met?[6]

3

4   c)   The narrative summary is the key component of this section. The current discussion

5   does not convey an understanding that the effects of chemicals are a function of

6   dose, exposure duration, and the background of the exposed individual.

7

8   d)   The proliferative effects section needs to be rewritten to clarify the last several

9   sentences that are on a different topic than the rest of the paragraph. The immune

10   surveillance point should be removed. The mutagenicity section could go one step

11   further to suggest a technique for the combination of disparate data sets (Brusick *et*

12   *al*., 1992). The primary problem in this section is that it is unclear what is necessary

13   and sufficient to suggest a plausible mode of action (see Scheuplein, 1995) for a

14   useful discussion of this area). The flexibility to this should be retained since this is

15   the strength of this version of the GLs.

16

17   e)   In the special subchronic studies section, it seems unlikely that doses in excess of the

18   MTD will be helpful in characterizing the biological effects and providing

19   mechanistic data for these assessments. In this case several points need to be

20   clarified. Do the data to be obtained support a specific tenet in carcinogenesis? Is

21   an oncogene over expressed, a tumor suppressor gene silenced, or an expression of

---

[6]"The available evidence may show that similar mechanisms are acting in humans and experimental animals. Of particular concern are those situations in which the possibility is considered of species-specific activity. One concern would be raised when humans are the more affected or susceptible species. This could be evaluated on the basis of knowledge of mechanisms and the comparative relevance of a mechanism to animal and human responses. Another concern is raised when the putatively unaffected species is human beings. Certain principles should be applied before such species-specific activity can be concluded. It should be established, (1) for the tumor site in question, that the mechanism in question is the primary one in the tumorigenesis in that species; (ii) that the same or a similar mechanism does not operate in humans; and (iii) whether the agent induces other types of tumors in experimental animals. If other types of tumors are induced, then (i) and (ii) would have to be fulfilled for each of them. Qualitative differences, in which effects occurring in one species are not expected to occur in another, should be distinguished from quantitative differences (such as different rates of biotransformation), which may influence only the degree of response rather than the presence or absence of a response." [IARC, 1991]

1   genes associated with cancer development altered? Is a secondary mechanism for

2   cancer development supported? The latter case permits one to link the induction of

3   tumors with a previously occurring event through a physiological or pathological

4   change that has a threshold.

5

6   f)   In section 2.3.5.3 of the GLs, the listing needs to be prioritized- genotoxic evidence

7   should be first, then the dose-dependence and temporal and spatial nature of the

8   effects should be documented. Both the biology and the statistical analyses should

9   be consistent and the biology should drive the assessment.

10

11   Selection of a single marker is insufficient evidence to link it causally to cancer. For

12   example an increase in cell proliferation that is not sustained or that is below a

13   certain level may be without risk judgments need to be case-by-case. Information

14   that helps to define the biological plausibility of the mode of action and not just

15   provide additional mechanistic detail is needed to support decision making. Rule out

16   mechanisms that are directly genotoxic and demonstrate a plausible link to

17   mechanisms that may not be operative at all doses. These studies must demonstrate

18   that the secondary mechanism exists in animals, that this mechanism can be

19   interrupted to block tumor development and that a no effect level for the secondary

20   mechanism exists. The second point is that the induction of hyperplasia and other

21   precursor lesions should be reversible upon cessation of the agent being tested

22   (Scheuplein, 1995). This is followed very clearly in the Appendix D thyroid

23   hormone example.

24

25   g)   In section 2.4, dose and duration of exposure need to be included along with biology

26   of the organism and chemical properties of the agent. Inputs to mode of action

27   section needs to be rewritten to reflect PK considerations, and remove the discussion

28   of TCDD on page 9. Figure 2-1 needs to be amended to indicate that in the absence

29   of all of the necessary data a default assumption of linear or nonlinear can be used.

30   The flexibility of this part is the key to the utility of this document. This entire

section needs to indicate that the effects of compounds are dependent upon the dose and duration of exposure to the agent and that the administered dose is of less relevance than the dose at the target site. The most relevant factors would be WOE, exposure conditions, and relevance to humans.

h)   Use of the mode of action data- the flexibility in this section is to be recommended.

g)   Remove sentences on "key event" this terminology is confusing since one is describing a process that is a continuum of biological response.

h)   The discussion on genotoxicity states that determining whether genetic damage occurs from chemical exposure is an important part of risk assessment. This section needs to speak to the method for combining data from many disparate studies and what the minimally acceptable criteria are for inclusion of a specific study in this context. It is also important to include a discussion of non-genotoxic effects that may impact on carcinogenicity. It is however insufficient to indicate that a chemical can alter gene expression with acute exposure without specifically linkage this change or chronic change to the carcinogenic potential. Transient alterations that can be reversed would in this context be of a lesser concern than chronic effects that can be linked in a temporal and dose-dependent manner with the induction of cancer. The that needs to be emphasized is that the effects of all agents are dose dependent.

Specific points which should be addressed in these sections include: what to do in the absence of a BBDR model for the chemical and endpoint of interest. The data should define whether linearity or non linearity is assumed. For example is the background incidence of tumors in the target tissue (for example mouse liver) is 20%, then why are we extrapolating to zero? Second, what should be done if the high and low dose give the same tumor incidence or if the high dose gives a lower incidence than the low dose? Or the most likely scenario in which there is no detectable biological response (i.e. no tumors at the low dose and an increased

1   incidence at the higher dose- how does this indicate a linear process. The lower
2   dose is statistically at most a 10% response that was not detected given the
3   constraints of the animal bioassay, but may be zero
4
5   i)   Decision criteria for judging adequacy of WOE for a specific mode of action need to
6   include both the biological endpoint and an appropriate measure of PK/PD to help
7   define default assumptions for the MOE.
8
9   j)   All of page 9 needs to be rewritten.
10
11   k)   Evidence of non linearity should include information on the biology of the response
12   under consideration. For situations in which both linear and non-linear components
13   of the assessment are required this should proceed based on the expected exposure
14   dose and duration. In dose range X, a nonlinear mode of action is most appropriate.
15   Figure 2-1 should be reconsidered to reflect that the default should be non linearity
16   and that the presumption of risk should have some biological support. The onus
17   should be to prove linearity.
18
19   l)   The listing in section 2.5 needs wordsmithing. The term key events should be
20   changed. The section on mode of action is fine in content but needs rewording. In
21   general, the writing style lacks precision. Obtaining precision should not eliminate
22   flexibility- the inclusion of more biology will strengthen the risk assessments
23   performed.
24
25   m)   The examples included in the GLs require additional refinement. Although it is clear
26   how the Agency intends for the MOE analysis to be performed, the discussion of the
27   uncertainty factor issue needs some careful revision.
28
29   n)   The appendix D portions are fine with the exception that in both the thyroid and
30   bladder cases a good analysis of potential human risk is not provided. On the GLs'

1 Page 8 (line 5) the number provided should be 1000 not 100. The last clause on
2 page 12 should be removed. If the animals were maintained on a caloric restricted
3 diet and lived for 3 years, the likelihood of female thyroid tumors would be limited.
4 The real issue here is the question of whether these tumors in rodents are predictive
5 of human cancer risk at doses achievable in humans (see McClain, 1995; 1992).

6

7 o) A paper (*Use of Mechanistic data in Assessing Human Risks from Exposures to*
8 *Particles)* (McClellan, 1997) offers a template for the conduct of research directed
9 toward reducing uncertainties in assessing human health risks from exposure to
10 particles. The guidance provided in this paper has broad relevance to developing
11 information pertinent to assessing cancer risks. It addresses:

12

13 1) the design of mechanistic studies
14 2) dose levels related to environmental levels for both *in vivo* studies and *in*
15 *vitro* studies
16 3) the use of dose levels for *in vitro* studies which provide a gradient of
17 response (relative to dose) and can elucidate how underlying mechanisms are
18 influenced by dose and dose rate
19 4) when practical, observations made with animal tissues studied *in vitro* should
20 be extended to human tissues
21 5) when practical, the results of mechanistic studies should be presented
22 quantitatively, within the framework of an exposure (dose)-time-response
23 matrix
24 6) investigators should place substantially greater weight on data obtained over
25 a range of exposure (dose) levels when interpreting mechanistic data for
26 carcinogenic classification schemes.
27 7) mechanistic data should be used for risk assessment purposes only when they
28 represent a mechanism operative in humans at plausible exposure levels

29

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A-6

p) There is confusion about what the MOE factors represent. Contributing to this confusion are the varying viewpoints, expressed in the draft GLs, on the point of departure. The draft indicates that the "ideal would be to identify the dose at which the key events just begin to occur in a heterogeneous, human population and to use that dose as the point of departure." Under this viewpoint, (one that some members of the Subcommittee supported), the point of departure would represent a population threshold dose, expressed as the equivalent human dose. The dose would reflect human and interspecies variability, differences in effect level doses associated with key events and tumor, and adjustments to move from ~~an~~ point estimate of the ED_{10} to a vanishingly small risk level. A major reason for this alternative viewpoint, is the potential confusion over the use of advisory MOE.

q) Ultimately, the issue of using the NOEL and point estimate of the ED_{10} versus the LED_{10} will need to be resolved with real data rather than with opinions. Hypothetical statistical arguments about how DR curves will vary under real-world conditions often yield us "attractive" curves that have no biological relevance. The next step is up to the researchers, who need to try out all these suggestions and illustrate for EPA what works well and what needs further work.

r) When the NOAEL approach is used to derive an MOE under these GLs (or if the LED_{10} approach is used without the steepness factor), the approach is essentially the same as that for non-cancer effects. However, the severity of the effects being addressed may vary widely (from cancer mortality to subtle sub-clinical effects). Although this specific use of a severity adjustment factor was not discussed at the public meeting, ~~TheSubcommittee believe~~ it would be reasonable for EPA to account for severity of the health effect under consideration. ~~E.g., for cancer this could be accomplished by explicitly including a factor to account for the severity of the cancer endpoint. This factor could be different for different types of cancer (e.g., non-melanoma skin cancer versus pleural mesothelioma).~~ If this approach is adopted, it is recommended that the Agency extend the procedure to similarly

1   account for relative severity of different non-cancer health effects. During the

2   preparation of this report, several Members did comment on the idea of adding

3   another adjustment factor to account for severity of the health effect. These

4   Members believe that EPA needs to be careful about adding factors with borderline

5   justification, because they cascade and lead to recommendations that lack credibility.

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